VOICES

PERSONAL STORIES FROM THE PAGES OF NIB

Research on COVID-19: Stories from IRB Members, Research Administrators & Investigators

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VOICES

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Contents

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Introduction
Research on COVID-19: Stories from IRB Members, Research Administrators & Investigators

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Abstract. This symposium is separated into two sections. The first includes twelve personal stories from IRB members, administrators, or staff about their experiences during the COVID-19 pandemic. The second section includes twelve personal stories from researchers. Six commentaries on these narratives are offered by experts in research ethics, regulatory oversite, IRB administration, the logistics of clinical research, and investigator responsibilities. These narratives and commentaries offer an inside look at how the COVID-19 pandemic affected the physical logistics of clinical research already underway, demanded immediate investment in scientific investigation of vaccines and treatments, and rerouted the usual decision pathways that guide ethical practice.

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Keywords. Bioethics, Clinical Trial, Common Rule, COVID-19, Human Research, Human Research Protections, Institutional Review Board, Medical Ethics, Narratives, Research Ethics, SARS-CoV-2

Introduction

In February 2020, Coronavirus Disease 2-19 (COVID-19) was an epidemic in mainland China. Numerous symptoms, such as fever, cough, fatigue, loss of taste or smell, nausea and body aches were mild irritations for some, but for others, these developed into life-threatening issues requiring hospitalization and ventilator pumps (Centers for Disease Control and Prevention, 2021). By the end of March, an alarmed World Health Organization declared a pandemic and an international travel advisory was in place (World Health Organization, 2020). It is believed that the first COVID-19 death in United States was on February 6th (Yan, 2021). Four short weeks after this, state, county and city governments were debating when and how to quarantine individuals and groups, and what

kinds of curfews were appropriate. The country began to panic.

As of mid-April 2021, 138 million people around the word have contracted COVID-19, and three million have died. There have been nearly 32 million cases in the United States, and over 570,000 deaths (Centers for Disease Control and Prevention, 2021). Government response to this health emergency has been inconsistent and at times, grossly politicized. In many ways, the American people were left to decide for themselves who to believe, what to do to safeguard their families, and how to maintain a sense of normalcy in increasingly restrictive and sometimes volatile public spaces. The consensus (for the most part) was that we could care for ourselves and our loved ones by social distancing, wearing masks, practicing good hygiene, and self-isolating when called for. (A few extra rolls of toilet paper never hurt either.)

Make no mistake, all eyes were on healthcare providers and the scienti c community. While nurses and doctors worked around the clock, often without adequate PPE and forced to ration resources and life-saving equipment, it became increasingly clear that we needed better treatment options and a vaccine, and we needed them as soon as possible. As Walter Dehority points out in one of the following narratives, "A drowning person will reach for any lifeline thrown their way, whether or not that line is secure." Misinformation abounded, but worse, unproven treatments became faddishly popular and sometimes assumed to be a new "standard of care."

The most publicized example of this is hydroxychloroquine, a medication used to prevent and treat malaria. The drug was the subject of an early clinical trial to test whether it could prevent illness or reduce the severity of illness in people who had been exposed to the virus recently (Boulware et al., 2020). Approximately two weeks after the trial began in mid-March of 2020, FDA issued an Emergency Use Authorization (EUA) for treating COVID-19. Despite warnings regarding the drug's effects on the heart, the pressure to find enough hydroxychloroquine to treat as many patients as possible continued (Shaw, 2020). Several studies were published claiming to demonstrate significan benefit to patients, but they were soon retracted (Locher, 2020). By the middle of June, the EUA was rescinded and trials using hydroxychloroquine to treat COVID-19 were halted.

This double issue of *Narrative Inquiry in Bioethics* explores the impact of COVID-19 on clinical research from several angles. First, what happened to existing studies, already opened and with enrolled patients, whose careful processes were thrown into disarray by reallocation of resources, social distancing, and health restrictions? Secondly, were research institutions, investigators, and IRBs supposed to evaluate and, maybe, "fast track" studies designed to meet an immediate public health emergency? Where there existing regulatory options that addressed these issues? Were they a perfect fit or was "good enough" acceptable? Were traditional best practices nullified by the staggering infection and mortality rates of this pandemic?

Not only were patients, clinicians, researchers, and politicians in a hurry, but so were medical journal editors. The pressure to publish COVID-19-related research and make "evidence" widely available as quickly as possible led to radical changes in publication practices. Routine peer review processes were abandoned, and papers were published online rapidly with minimal review. Even the most prestigious and highly ranked medical journals published poor quality papers, including some based on clinical trials that had included very few people or, in some cases, the data on which numerous papers were based were highly unreliable and possible fabricated (Teixeira da Silva et al., 2020). An extraordinary number of papers have since been retracted or have been subject to editorial expressions of concern (Retraction Watch, 2021); Boschiero et al., 2021). In addition to publishing rapidly through journals, many papers were made available as preprints, which, as medRxiv, the preprint server for health sciences, describes on its website, "are preliminary reports of work that have not been certified by peer review"(medRxiv 2021). It cautions that, "They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as

established information." Yet, time and time again, the media disseminated preprints, and clinicians and politicians relied on them to advocate for new treatments and highlight "breakthroughs" and "discoveries." Some of these papers were silently withdrawn.

Retractions, expressions of concern, and withdrawals of papers often receive far less attention than the initial publications. They can have long-lasting harmful effects. Not only does continued reliance on such publications expose patients to risk, but they can undermine and impede future research and contribute to a general mistrust in science

The Belmont Report is meant to be our compass (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). Considering respect for persons, beneficence, and justice take us very close to the understanding of what *should* be done but falls short of practical guidance for exactly *how* to do it. Over the years, many have suggested other, less abstract principles that might assist with this, things like responsible stewardship, accountability, and transparency (Presidential Commission for the Study of Bioethical Issues, 2011). The people who *act* on these concepts are the focus of this double issue: the investigators, research teams, and IRB administrators, staff and committee members. In these pages, they share with us what it is like to apply these principles to clinical research under immense personal and professional stress, and how they addressed the possibility of modifying traditionally held ethical guidelines in the face of a global health emergency.

The Call for Stories

The 24 stories in this symposium—12 from researchers and 12 from IRB members, administrators, and staff —describe a range of experiences conducting and overseeing biomedical and behavioral and social sciences research on COVID-19. We included 5 additional stories from researcher and 4 additional IRB members, administrators, and staff stories in the online supplement for this issue.

Typically, *Narrative Inquiry in Bioethics* drafts and advertises a call for stories. The process for collecting stories for this symposium was different. The Bioethics Research Center (BRC) at Washington University in St. Louis received funding from the National Institutes of Health (NIH) to conduct an online survey of researchers and IRB members who conduct or review research on COVID-19. The purpose of the survey was to gain feedback from researchers and IRB members to understand more about the potential ethical, oversight, and regulatory barriers to COVID-19 research. The BRC recruited IRB stakeholders through Public Responsibility in Medicine and Research, PRIM&R, the largest national organization serving IRB staff members and board members. The project team asked these IRB members to forward the links to the recruitment text to researchers. They also recruited through the CTSA network, public health listservs, lists of chief research of cers and deans of research derived from publicly available websites, and publicly available information on clinicaltrials.gov. In the survey, participants were asked if they would be interested in writing and sharing a story on their experiences during the COVID-19 pandemic in the journal *Narrative Inquiry in Bioethics*. Participants who indicated they were interested were asked to provide their name and email address, which were kept separate from their survey responses, so that they could be recontacted by the project team.

We (the two symposium editors) reviewed de-identified survey responses from participants who said they were interested in contributing a story. We settled on a group of authors to invite (20 from each group). We drafted and finalized a call for personal stories from IRB members, administrators and staff, and researchers about their experiences during the COVID-19 pandemic to send along with an email invitation to write a story. The BRC project team re-identified the survey participants whose responses were selected by us and they sent invitations to those authors to write an 800 to 2000 word story for NIB.

The call for stories was also posted on the NIB website. Two stories were sent by people who had

not completed the online survey but saw our call on the NIB website or heard about the call through colleagues. Some participants who initially were interested in writing a story reconsidered the time commitment or declined because they worried about workplace retaliation, despite our offers to help them with anonymization. The BRC team sent out additional invitations: 64 in total to IRB members, administrators, and staff and 86 to researchers. With these invitations, the research team offered to send participants their survey responses to help them draft their story. A total of 24 researchers and 20 IRB members, administrators, and staff requested their survey response.

We sought stories from individuals who had proposed, conducted, or reviewed COVID-19-related research. We were interested in hearing about struggles and successes, frustrations and triumphs, challenges and solutions. We wanted to learn how structures, relationships, and policies and practices advanced or hindered research, how problems were identified and resolved, and the kinds of difficultie that went unaddressed. We encouraged authors to give readers an idea about the personal experience and effects of being engaged in COVID-19 research and oversight. Finally, we invited authors to identify lessons that pandemic research might reveal to improve human research protections programs and research practices.

Authors were asked to consider the following questions:

- For researchers: What kind of research were you conducting? What COVID-19 problem did you seek to address? What research approach or innovation did you propose?
- For IRB members and administrators: What kinds of research were you responsible for reviewing or overseeing?
- What ethical, regulatory, or institutional policies or challenges did you face? How did you respond to them?
- What advice or recommendations do you have for IRBs that review research on a pandemic illness such as COVID-19?
- What advice or recommendations do you have for researchers who study a pandemic illness such as COVID-19 to help them ensure compliance?
- What else would you like to tell us about your experience of conducting, reviewing, or overseeing research during the pandemic?
- What would you like people who develop policies and laws to know about the needs of caregivers?

The IRB members, administrators, and staff were quite willing to share their experiences. There was a sense of catharsis in some of answers to the original survey, as if the respondents had been looking for a way to process the drama that had been suddenly projected onto their normal operations. They easily transformed their short answers into narratives about the tension between regulations, institutional policies, and an unprecedented public health emergency—and reflected on how personal and societal distress affected almost every action they took.

Several researchers who indicated a desire to share stories reached out to discuss their experiences by phone. They shared experiences about institutional missteps, politics, and how concerns about public image undermined both clinical care and research during the pandemic. In the end, some of these authors understandably chose not to contribute stories, even anonymously, for fear of being identified. This was not surprising, yet it was disappointing. Nevertheless, the stories here from researchers reflect a wide range of positive and negative experiences, including people who encountered hostility to generating knowledge through research or to collaborating across institutional or other lines.

The Narratives

IRB members who wrote narratives for this symposium include a committee Chair, senior administrators, a new staff member, committee members, and several people who wear more than one hat. A couple of the authors highlight ethical challenges associated with "pandemic research" and "research during a pandemic," while others focus on the logistics of switching to remote meetings and creating or maintaining open lines of communication. Many stories point out that the pandemic exacerbated existing systemic weakness and which, because of

the emergency, were (finally) addressed. Most stories express satisfaction with how their IRBs rallied to overcome obstacles and were, ultimately, able to provide ethical and timely review of COVID-related protocols.

The researchers who shared their stories with us include physicians, psychologists, and scientists whose work involves clinical trials, observational research, and surveys and other social science methods, among others. There are many stories of researchers who found research administrators and IRB offices and other colleagues to be flexible, supportive, and collaborative. Sometimes this was characteristic of their prior experiences with those entities and sometimes not, in which cases researchers were pleasantly surprised. Other narratives focus more on the experience of conducting research, whether in the clinical setting or online, and the advances and setbacks they faced.

The Commentaries

This symposium includes three commentaries on the stories from IRB members, administrators, or staff and three commentaries on the stories from researchers. The commentaries draw out themes and lessons learned from the narratives. These commentary authors include experts in bioethics, research ethics, health law and policy, medicine, health informatics, minority health and clinical trials.

Jerry A. Menikoff, MD, JD is the Director of the Office for Human Research Protection, within the U. S. Department of Health and Human Services (HHS). This office is responsible for protecting the rights, welfare, and well-being of subjects involved in research conducted or supported by HHS. Dr. Menikoff has also served as the director of the National Institutes of Health (NIH) Office of Human Subjects Research and held numerous academic positions. Dr. Menikoff writes as an individual and not in his capacity as an employee of the U.S. Government.

Sumit Mohan, MD, MPH is Associate Professor of Medicine and Public Health at Columbia University in New York. Much of his current research focuses on improving access to and outcomes of renal transplantation among minorities and improving organ allocation. He has taken care of patients with COVID starting from the spring surge in New York, developing strategies of care in the presence of supply chain constraints and leading the COVID clinical research effort for the division of nephrology while also contributing to broader efforts in predictive analytics.

Gianna McMillan, D. Bioethics, has served on many IRBS and currently sits on the FDA's Pediatric Advisory Committee. Dr. McMillan teaches for the graduate program at the Bioethics Institute at Loyola Marymount University in Los Angeles. Her most recent interests involve the use of personal narrative as a teaching tool and working with biostatisticians to create patient-friendly explanations about the ethical use of innovative trial design.

Bruce Gordon, MD is a professor in the Division of Pediatric Hematology/Oncology at the University of Nebraska Medical Center (UNMC) in Omaha, Assistant Vice Chancellor for Regulatory Affairs, Vice Chancellor for Research, and Executive Chair of the Institutional Review Board. UNMC has the largest biocontainment unit in the US and was at the forefront of caring for and conducting research on patients with Ebola in 2014, efforts in which Dr. Gordon played major roles. UNMC once again was involved in early research on testing and treating Sars-Cov-2 under his leadership.

Wilson Jackson, M.D., is board certified in internal medicine and gastroenterology and hepatology and sees patients in private practice in Pennsylvania. He also has experience working in academic medicine, has held leadership positions in multiple medical societies, and developed technology to help improve the care of patients with eosinophilic esophagitis.

Ana S. Iltis, PhD, a co-editor of this symposium, provides a third commentary on these narratives. Dr. Iltis has expertise in human research ethics and is involved in research projects that faced significan slow-downs due to the disruption of health care during the pandemic.

Conclusion

This symposium looks at the unique environments of research during a health emergency from different perspectives. Frustrations are expected. The authors are candid about concern for their personal safety as they struggle to meet their professional responsibilities. They worry about doing the "right" thing in both regards. While the narratives are offered in two groups, several themes are woven through the collective: surprised distress, the need for flexibilit , the importance of communication, and the fear of doing too much too soon—or too little too late. Above all, there is a solid foundation of dedication. These researchers, these committee members and staff, are accustomed to pulling together to explore scientific avenues that will safeguard the health of the general public. The COVID-19 pandemic presented obstacles that were (are) at times, wildly dramatic—even traumatizing, but this did not change their motivation, their work ethic, or the rigor of their ethical reflection

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Personal Narratives From Investigators

Gary Schiller, Westyn Branch-Elliman & Paul A. Monach, David Altschul, Eric Lenze, Lauren T. Southerland, Jennifer A. Frey & Russell Williams, Barbara P. Yawn, Todd B. Seto, Rebecca Erwin Wells, Laleh E. Coté, Rebecca C. Hendrickson, Patrick W. Romani, Beth Prusaczyk, Yuan-Po Tu, Francisco José Barbosa Camacho, Carl Asche, Mohammad O. Almoujahed, Sharjeel Ahmad, Anthony Dwyer, Sarah Stewart de Ramirez, Emanuele Chisari, Javad Parvizi, and Michael Korenfeld

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Personal Narrative About COVID-19 Research

Gary Schiller

I direct a clinical research program in Hematological Malignancies and Hematopoietic Cell Transplantation. On a practical level, this means that I direct a team of nine, soon to be ten people, who perform regulatory, data management, research nursing, and research coordination for about 25 active clinical trials, and about 20 more trials awaiting activation, or closed to accrual. We work with patients with diseases as diverse as myelodysplasia, acute leukemia, multiple myeloma, and bone marrow and stem cell transplantation. Our group also includes several younger faculty members and is self-contained, by which I mean that I developed the funding model that supports the personnel. We do not receive funds from the university to run the program. In a normal year, we accrue about 50 or sometimes 60 patients per year into these trials.

At the start of the safer-at-home orders, it was challenging to conduct clinical research, but it was essential. The worst scenario that we had to confront was the closure of studies for some of our most vulnerable patients. This might have been done because meeting certain endpoints, such as study visits, became difficult, although doable with telemedicine. But the major reason that studies were shut down, in my opinion, did not have to do with study-related visits, which continued since our hospitals and clinics were open, but due to monitoring problems. Closing studies due to regulatory challenges was, in my opinion, the wrong thing to do, and I said so at the time, not just now, in the sunlight of looking retrospectively at the situation. The reason it was wrong is that diseases don't disappear by virtue of a pandemic. Even during a crisis, cancer does not take a break, so sponsors who closed studies did so at the risk of ever achieving accrual targets and did a disservice to our patients. I sure hope that, when these studies are completed and results published, editors of journals require a statement in the methods section of the paper documenting whether there was a hold period for the study. I bet that this recommendation will be met with resistance, even if behind closed doors! Also, monitoring was hit hard by the crisis, as I described above. Ultimately, the institution determined that monitoring could be done electronically, with safeguards in place to protect confidentiality and to restrict access to personal information, but

this took a few months, and mechanisms for safe monitoring to continue to be developed.

When the initial lockdown came, around March 12, 2020, we were confronted with safer-at-home orders but no guidance regarding research studies. Because our patients do not have the luxury of scheduling their diseases outside a pandemic epoch, we had to work around restrictions imposed by the County and the University. We somehow did that, and maintained many of our trials, and have accrued about 50 patients to our studies as of November 1, 2020. I was offered participation in several multi-center studies from industry for COVID-19 therapy based on drugs that we had used for patients with hematological malignancies and transplantation. Although these drugs were developed in a cancer setting, their mechanisms of action offered potential efficacy outside neoplasia. I turned these over to my colleagues in Infectious Diseases who are coordinating the research strategies of this academic institution. I did attend several conference calls prior to initiation of the studies, feeling some responsibility for bringing them here.

The challenges to our research initially consisted of the safer-at-home orders that did not defin research personnel on clinical trials as essential workers. Fortunately, I was able to come to my office daily, and since I run a large clinical research program, I was able to supervise those studies still accruing patients. My team of physicians and I also consented many subjects, and my team of two research nurse practitioners and one study coordinator screened them. Many have gone on research protocols at this time. However, not having the regulatory staff on-site proved very difficult. Although they worked from home, many things were not done in a timely manner, documents were not signed, and amazingly, there were no easy electronic options. For example, FDA 1572 forms could not be signed electronically. Data management was doable from home, but interfacing with regulatory bodies in the academic structure was not easy and we could not furlough employees, so I, and the few of us on-site, did the bulk of the secretarial work—printing out forms, signing them, sending them electronically, etc. I have no idea whether any of these documents are being filed, and I know that we did not receive anything through the mail for months. Presently, we get mail about once a week, but the backlog is immense. Finally, after 3 months of confusion, we developed a rotation system by which all personnel were assigned days to come into an office, without other personnel present, in order to complete their work, answer phone calls from patients or trial subjects, provide support to the research nurses, and electronically meet with monitors.

IRBs and researchers will need to develop different standard operations based on what was learned during this critical period. Either we have to develop a system of electronic signatures, or a delivery system for hard-copy signatures. The research infrastructure will need to assess the value added by scientific peer review, by coverage analysis, and by contracts, by reviewing the large number of outside serious adverse events sent, pro forma to investigators, and the overhead costs of all those personnel who may be working from home. Zoom or other electronic platforms provided some help, but in the end, they merely added to the work of people on-site who ran multiple functions. Even today, I am writing this essay while intermittently checking email and while attending an on-line international academic meeting! The logistics of all the juggling of multiple responsibilities actually required more staff on-site, not fewer, and left many of us wondering whether our staffing models were correct prior to the pandemic.

Not What Anyone Signed up for: Unnecessary and Insurmountable Barriers Encountered in Conducting Clinical Trials in COVID-19

Westyn Branch-Elliman & Paul A. Monach

WBE's perspective

My 2020 started with an email entitled, "Happy New Year! Have You Read about this Virus that's Coming to Kill Us All?"

I remember the last day my life was "normal." It was the end of February, 2020 and I was on the phone with my father, and he was asking me my

thoughts about what we were seeing in the news about the novel coronavirus—then still regarded as a distant enemy in a faraway land. By way of background, I am an infectious diseases specialist with training in epidemiology, infection control, and implementation science. In the past, I was a hospital epidemiologist, in charge of local outbreak control, and more recently, I work in clinical research, focusing on weighing risks and benefits of different infection prevention and antimicrobial use strategies and on expanding infection prevention services to relatively uncovered aspects of the healthcare system. My father was calling to ask me my thoughts about the short- and long-term prospects for an epidemic in the United States, and what my thinking was on how this might impact the financial markets. In the middle of the call, I received word of the first "suspect case" in our hospital. I abruptly hung up the phone and did not look back. In fairly short order, cases began to peak, schools closed, my elementary school-aged children were suddenly house-bound, and the state was put under near-lockdown. I did not have another day "off" until sometime after Memorial Day.

PM's perspective

I remember exactly where I was on the morning of September 11, 2001, and also when I heard that the *Challenger* had exploded in 1986. I had no "COVID moment," but over the course of March my obsession with the pandemic grew exponentially until it peaked at the point of controlling everything I did other than activities of daily living (ADLs). I knew I would be low on the list of people to be called in for "risky" inpatient work, having one of those "pre-existing conditions," but I had to *do* something; with apologies to the patients I take care of at the VA who really did risk their lives for something in the past, I had to enlist. The opportunity arose when Westyn, whom I knew only because we served together on the local institutional review board (IRB), asked for my input on the use of rheumatologic drugs, specifically hydroxychloroquine and tocilizumab, in an institutional "treatment guideline" she was developing to advise inpatient teams on what labs to follow and what medications to use, based on very limited anecdotal evidence, to help the droves of patients we expected to descend on our hospital. As it turned out, my experience with clinical trials, including the plethora of bureaucratic processes and acronyms and numbered forms, would come in handy. Strangely, one of the few specific times where I remember where I was is when Westyn called to tell me she was being pushed to do a clinical trial.

WBE and PM: Designing and Implementing a Clinical Trial

In March, faced with a deadly disease descending upon our city and our hospital, there was an urge to be able to offer our patients "something" beyond the under-appreciated supportive care. Clinicians widely acknowledged that no available drug had sufficient evidence to support indiscriminate use in a purely clinical setting. The question was whether to use medications off-label based on limited anecdotes or to conduct a clinical trial—the firs of many ethical issues we have confronted in the half-year since then. There was a desire by many, both among research leaders and some clinicians, for a "clinical trial" banner, so that patients would be appropriately informed about the potential for a lack of benefit—and potential for harm—associated with almost any COVID-19 intervention. With these realities in the background, the two of us, both clinical researchers and members of our facility's IRB, received our marching orders: designing and implementing a clinical trial in time for the "first wave." Why were we chosen? Partially because of our position on the IRB—one of the providers assigning us this Herculean task specifically said, "We picked you because we think you are the only ones who will be able to get the paperwork approved."

Under normal circumstances, the process of designing, refining, and conducting a clinical trial would take months, at least. However, with COVID breathing down our necks, time was short. We reviewed the evidence available, limited to advice from our more experienced overseas colleagues—and then found ourselves constrained by which medications were available for purchase. We were lucky to have pre-existing relationships with the important institutional stakeholders—including the leaders in Research and Development, the clinical trials Coordinating Center, the IRB, and the

pharmacy—to move the trial from conception to implementation. We designed a pragmatic, adaptive randomized controlled trial comparing the addition of IL-6R inhibition to standard care for hospitalized patients with a confirmed diagnosis of COVID-19. With members of the team working literally around the clock—emails and approvals were flying during the hours between 2 and 4 AM—we were able to advance from a 2-page summary "pitch" to IRB approval in 6 days and enrollment of the first patient 4 days late .

After securing a medication amidst supply chain barriers, which necessitated completely revising the study within the 6-day period of design, the regulatory and ethical challenge we noted immediately when moving the study to the real world was: how do we weigh the research requirement for documentation of informed consent against the need to keep staff safe, while also limiting use of personal protective equipment (PPE)? Problems with PPE shortages in the clinical setting are well-known, but the impact on the research service line is not. Although questions about whether a wet signature was required were under review, all agreed that the patient should receive a paper copy of the consent form. A member of the staff doing this strictly for research purposes would risk exposure and have to use PPE to simply hand the sick and potentially morbidly ill patient a 7-page stack of paper—at a time when providers were instructed to wear their masks "for as long as possible." We solved this first dilemma through collaboration with our clinical colleagues, who were working in the COVID units. They agreed to bring the consent forms to the patients' bedsides during morning rounds, so that we could avoid redundant exposures and use of PPE.

After the dust settled on the problem of delivering a paper copy of the informed consent form, we experienced another: what were the requirements for the informed consent processes? As a VA facility, we are required to abide by FDA regulations, but early in the pandemic, when we were at our peak caseload, these "regulations" (technically Guidances) were muddy at best. During an early online presentation, we were heartened to learn that the FDA would allow a remote consent process, with an impartial phone witness signing the consent form to af rm the patient's desire to participate—a process not dissimilar to what has led to the highly successful RECOVERY Trial in England. This appeared to solve our PPE and staff risk problem: we could conduct the entire process over the phone, not worry about "poison paper" (that was more of a concern then than it is now), and limit exposures. Unfortunately, only a few weeks later, the FDA issued an update clarifying that the witnessed consent process could only be used for clinical consents, not research consents (particularly in interventional trials), and we were forced to develop more complicated and cumbersome processes, all in the name of collecting proof of a wet signature on a page from the patient or legally authorized representative (LAR).

Which brings us to the third, and most troubling, major ethical issue we faced: therapeutic misconception. One of the tenets of conducting clinical trials is that there should be "clinical equipoise," and in line with that, patients should be deterred from expecting benefit from participation. Our experiences conducting a trial in COVID patients laid bare why these concepts are unrealistic, particularly for fatal diseases with no known effective treatments, such as COVID-19 in elderly patients. High mortality coupled with lack of evidence creates a perfect storm: patients and providers desperate to receive or prescribe "something," whether in the context of a clinical trial or not. No one was willing to accept the idea that they would just let patients die without trying to do something more than the "supportive care" recommended in early societal guidelines.

Research consent processes require that investigators emphasize to patients that they may not benefit from participation in a clinical trial. However, this concept is divorced from reality: except for comparative-effectiveness studies, the reality is that patients participate because they hope for benefit, and providers refer their patients because they hope that the trial will help their patients more than will standard care. We encountered this challenge first-hand during our own trial. Because our study included a standard care arm—meaning no active therapy—we witnessed psychological distress not only among patients and their relatives, but also among treating physicians as evident in immediate abandonment of the scientific principles that they had supported during design of the trial. When

patients were randomized to standard care, physicians quickly revolted, and requested open-label use of the unproven study drug within 24 hours—even in stable patients. Honestly, we felt the same thing ourselves: as a clinician, and even as a researcher, it is very difficult to tell a patient that you have nothing to offer them, particularly when you feel responsible for that limited choice. Plus, we have been on the other side.

WBE

At age 33, I was diagnosed with early-stage, HER-2 positive breast cancer. Because of my "extremely" young age, and the aggressiveness of the tumor, there was a long discussion about how I should be treated: Standard chemotherapy regimens? Clinical trials? Something else? My oncologist and I considered enrolling in a clinical trial of chemotherapy plus Herceptin versus TDM-1, a newer, more expensive option that linked the chemotherapy agent to the Herceptin. The upshot of the trial for patients was that TDM-1 did not cause hair loss, and based on trials in other populations, there was hope that the medication would be more effective than the current standard of care. The prospect of avoiding hair loss is a big draw for most cancer patients, and especially young women: no one wants to look "sick." In this trial, patients, with high hopes of not losing their hair, and for the opportunity to receive a potentially more effective therapy, were randomized 3:1 to the novel treatment arm. Not surprisingly, despite being fully informed about the possibility of randomization to the standard of care arm, patients randomized to the taxol-herceptin arm were disappointed—they were hoping for a better drug, fewer infusions, and a tangible benefit (no hair loss) that they didn't receive.

Ultimately, I was conservative and opted for a standard (and more aggressive, although not the most aggressive) chemotherapy option, and lost all of my hair. Having been through that trauma and having to walk around that way for far longer than I ever would have imagined, many years later, I followed up on the trajectory of the trial, and learned that it did not meet its primary endpoint of improved safety in the TDM-1 arm, although interestingly, one of the important "clinically relevant toxicity" endpoints—hair loss—was not included as one of the measured adverse events.

PM

I spent the first two months of COVID in Boston with a WBC count averaging 3000 cells/uL, a lymphocyte count averaging 900, and transaminases high enough that I would have been kicked out of a clinical trial of any drug on the basis of hepatoxicity. The offending drug was probably lomustine/CCNU, although procarbazine was also in play. The reason I had been taking them since October was that the low-grade glioma in my right motor cortex, initially dormant after treatment with temozolamide in 2013–14, was growing again. These treatments, along with the proton radiation therapy I received in 2019, are the only standards of care, and on average they are effective—temporarily. The median survival after diagnosis of a low-grade glioma with a favorable cytogenetic profile is 15 years, with a steady ongoing risk of transformation rather than some period of risk after which one is safe. At some point I am going to need a different treatment. It is of more than academic interest to me for new treatments to be studied, so that another proven approach is available when I need it. I would prefer that companies not be deterred from studying such treatments by the regulatory burden. If I need a treatment that is still in the investigational phase, I would prefer to not have a high risk of randomization to placebo, or to be excluded from the study based on having already received standard-of-care treatment—design elements often included because that is what is most likely to meet FDA requirements with the smallest number of patients.

WBE and PM: Even the Curse of the Billy Goat Will Be Broken

When it comes to serious diseases, patients enroll in clinical trials with the hope of bene t. Pretending otherwise and adding barriers to try to ensure this does not happen is a fool's errand. Use of placebo controls can avoid immediate psychological distress in addition to bolstering scienti c validity for subjective outcomes, but the use of placebos in diseases in which standard care is inadequate is

Table 1

Ethical issues that have arisen in the planning and conduct of our clinical trial.

1. Should we provide approved medications off-label or conduct a trial? Our original plan was to give tocilizumab IV in a sensible manner to very sick patients and be alert for new literature, rather than conducting a trial.
2. How could we maximize the amount of study drug available for the trial? In order to retain as much tocilizumab as possible for IV use, whether in a trial or open-label, one of us (PM) obtained the names of the small number of patients who normally receive tocilizumab IV monthly and contacted the prescribing MDs and asked them to consider switching the patients to self-injected tocilizumab every 1–2 weeks.
3. What was the most ethical trial design? When conceiving a trial design, we wanted to maximize benefit to participants while obtaining scientifically valid information to help future patients. We chose a "randomized play the winner" design with two active arms (tocilizumab and anakinra) and one standard-of-care (SOC) arm.
4. What was the most ethical trial design in the face of drug shortages? As the protocol was being finalized, we learned that neither anakinra nor tocilizumab was available in sufficient quantities to conduct the trial. We rapidly changed the design to a 2-arm trial of sarilumab (an anti-IL-6R antibody similar to tocilizumab) versus SOC. This decision forced us to allocate a larger proportion (50%) of patients to SOC at the start and design a trial similar to many being conducted around the world, rather than asking a novel and important research question.
5. What was the most ethical trial design to open the trial quickly? We chose to use sarilumab in its usual form (200 mg delivered subcutaneously via a pre-filled syringe) so that we would not risk needing to go through the time-consuming process of operating under an Investigational New Drug application (IND) from the FDA. This meant using anti-IL-6R treatment at a lower dose and less-aggressive means of delivery than what had appeared in the anecdotal literature.
6. How should we respond in the face of regulatory barriers that impede research? When one of us (PM) pushed later, based on press-releases rather than scientific publications, to increase the sarilumab dose to 400 mg, the FDA initially refused (6 days after being asked) to grant an IND exemption even though the drug's manufacturer had trials in progress using that dose, and then assigned us to a pre-IND process that is used to assist developers of new drugs with trial design. We determined for ourselves and then convinced the FDA that this was unnecessary (6 days), then rapidly (within 2 days) submitted an IND, and 14 days later were granted the exemption for which we had argued previously. The study was thus on hold for 28 days while awaiting decisions by the FDA, during which many patients who would have been eligible could not be enrolled. Initially we were averaging almost one enrollment per day. Since re-opening the study, we have not enrolled another patient for 4 months, because the disease has temporarily abated in our region.
7. Why is it important to make trial results available as soon as possible? The two announcements that led to changing the dose in our protocol—one reporting discontinuation of the 200 mg arm in the manufacturer's own study of sarilumab, and another reporting benefit of IV tocilizumab at a high dose analogous to 400 mg sarilumab—have not yet been followed by publications even in pre-print form. Subsequent announcements by the manufacturers of sarilumab and tocilizumab have reported negative results overall, in studies that included large numbers of intubated patients. The details, not yet available to the community, are relevant because the patient population targeted in our study (requiring oxygen but not mechanical ventilation) has been the one most frequently showing benefit, even if only minor benefit, in studies of other drugs.
8. What expectations do patients, family members, and clinicians have regarding fidelity to a research protocol? During the short time our trial was enrolling, we heard about expressions of disappointment from patients' family members when the patient was randomized to SOC. Also, our colleagues on several occasions wanted to use a "rescue" dose of sarilumab (which was in the protocol as an option in either group before the protocol was amended to change to a single, higher dose) within 24 hours of randomization to SOC, or to use the small stockpile of IV tocilizumab that was available for use outside the trial.

Table 1 (continued)

Ethical issues that have arisen in the planning and conduct of our clinical trial.

9. How should informed consent be obtained in the face of a pandemic in with PPE is in short supply? We felt it was important to avoid direct interaction with potential subjects if done strictly for research purposes, to avoid risk of infection with SARS-CoV-2 and to conserve PPE for clinical use. This meant that informed consent had to be done by phone one way or another, which we would guess is inferior to doing so in person.

10. Which members of the study team should be available to perform the informed consent process? The informed consent discussion was conducted by phone after a full copy of the form was delivered to the patient (by clinical staff) and legally authorized representative (LAR). The LAR was always off-site, because visitors were not allowed in the hospital. Because the process was laborious and we had other patient-care duties, consent was usually obtained by research nurses on rotation to be available 24/7. Although they know general internal medicine and the study protocol in detail, this process meant that the members of the study team most knowledgeable about the disease (WBE) and the study drug (PM) were not immediately available in the event of detailed questions.

11. How should informed consent for patients lacking decisional capacity be obtained? Most patients were determined informally to be incapable of providing consent. In the case of patients who had been transferred from an inpatient psychiatric facility, the study team made the decision on several occasions to not even approach the patient about participation, based on reports of aggressive behavior and non-compliance with SOC measures such as supplemental oxygen. In the case of patients with dementia, which was typically exacerbated by COVID-19 disease and accompanied by somnolence, consent was obtained from the LAR by phone, without involving the patient significantly in decision-making.

12. How should an agent be allocated when it is in short supply? Separate from the trial, WBE sometimes discouraged colleagues from using the hospital's limited supply of tocilizumab for patients who were reported to have advanced dementia at baseline, although there were no strict rules and decisions were made on a case-by-case basis with multiple physician review. In addition, clinical guidelines issued by VISN1 (the regional VA administrative unit in which VA Boston lies) and several other local medical centers advised initial use of tocilizumab at lower doses than had been used in China and Italy, due to low availability.

13. What should constitute valid documentation of informed consent? FDA guidance regarding the process and documentation of informed consent were cumbersome and had to clarified over time. The VA Office of Research and Development (ORD), in detailed discussions with the FDA, received clarification that physical evidence of a signature by the patient or LAR on the informed consent form had to be obtained and stored. We had already enrolled all 9 patients by that point, usually with oral consent by the LAR who reported having received and read the ICF and had no further questions. We are concerned, going forward, that placing the LAR in a position of having to return a photo or scanned signature page in a secure manner places undue burden under stressful circumstances and may exclude from participation persons without access to the necessary technologies.

14. Are the usual processes for obtaining and documenting informed consent slowing the progress of research and identification of effective treatments? VA ORD requested and received direct clarification of FDA policy. IRBs at academic institutions have all looked at the FDA guidance and made their own interpretations. We suspect that many institutions allowed the process that we originally followed (delivery of the full ICF to the patient or LAR, a consent process witnessed over the phone by an impartial third-party, and assurance that the patient wished to participate but without a requirement to return a signed form as documentation) and that many trials conducted in the US would not have been completed otherwise or would have excluded patients of low socioeconomic status and/or advanced age. In contrast, the RECOVERY study conducted in the UK explicitly allowed oral consent if written consent could not be obtained by the means required by the FDA [www.recoverytrial.net/for-site-staff/site-teams, www.recoverytrial.net/for-site-staff/site-set-up-1/recovery-trial-faqs-for-study-sites/#identification], and it enrolled 10-fold more patients than any US trial in the same time.

Table 1 (continued)

Ethical issues that have arisen in the planning and conduct of our clinical trial.

15. How can we balance rigor, patient protections, feasibility, and the urgent need to identify effective treatment? The RECOVERY trial is also pragmatic (simple eligibility criteria and outcome measures, no collection of samples for research purposes) and adaptive (data are interpreted after pre-specified numbers of patients have been enrolled), although the absence of a shared electronic health record meant that the study could not be embedded and required completion of electronic case report forms at the sites. The UK's single National Health Service (NHS) owns the hospitals and employs the physicians and staff, so contracting was simplified and non-negotiable. The list of study staff at the 176 participating hospitals occupies 17 pages in the supplementary appendix of the peer-reviewed paper, funded by a grant of only 2.1-million pounds beyond the substantial core funding already in place to support research infrastructure. During the first phase of RECOVERY, 15% of all eligible patients in the UK were enrolled. The Chief Medical Officers of the NHS are hoping for 60% enrollment now that case numbers and the associated burden on the clinical workforce are lower.
16. What roles do practicality, feasibility, and speed play in the ethics of the conduct of clinical trials? One of the differences between the pre-print of the study of dexamethasone in RECOVERY and its publication after peer-review is that a statement in the discussion about the speed of the conduct and analysis of the study was changed from "just 98 days" to "nearly 100 days." We presume that a reviewer or editor thought it was important to make this indisputable fact sound less impressive than it is. We are relieved that the statement describing the time between protocol approval to dissemination of results was allowed to remain at all.

also ethically problematic. Rather, we as a medical research community should recognize motivations behind treatment decisions and adjust how we conduct interventional research accordingly.

We will also add: cumbersome and changing recommendations, put in place by people who never have to interact with a patient or treating physician, has made the conduct of our trial nearly impossible. Everyone who could in uence the trial from a distance slowed it down. Everyone whom we knew personally or was within one degree of separation was incredibly supportive and helpful. We are extremely grateful to our friends and collaborators on the IRB, R&D leadership, the coordinating center, the pharmacy, and at other VA sites in New England, who worked tirelessly and off-hours in order to bring an option—any option—to our patients. Without them—and without the underlying trust we had all established as members of a group—the study would never have opened.

In the end, in addition to being grateful, we are exhausted, over-saturated with information about SARS-CoV-2, and more than a little bit angry. But we are also motivated to effect change. Advocates of pragmatic trials and learning healthcare systems have been arguing that the need for change, on ethical as well as scienti c grounds, is *urgent*—since at least 2015. Since that time, how many patients have we literally "protected to death"?

2020 started with an email about a new virus that was coming to kill us all, and then has featured thousands of emails related to our efforts to keep that from happening, which brings us to our nal question: Can we start 2021 with a different email: "Happy New Year! We have new treatments and a vaccine!"? For decades, the best year in Cubs' history was "next year." And then they won.

Author's Note: This story was submitted in October 2020. Much has happened since then, including that the trial re-opened and is nished, and the US has widespread availability of effective vaccines.

Related Work

Branch-Elliman, W., Lehmann, L.S., Boden, W.E., Ferguson, R., & Monach, P. (2020). Pragmatic, adaptive clinical trials: Is 2020 the dawning of a new age? *Contemporary Clinical Trials Communications, 19,* 100614. doi:10.1016/j.conctc.2020.100614

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Clinical Research Through the COVID-19 Pandemic: Crisis Response, Consequences and Innovation

David Altschul

Usually, I am a dual trained open and endovascular neurosurgeon. While working at a prominent academic medical center in New York City, my main focus has always been clinical care first. This all changed at the beginning of March 2020, when our city became inundated with patients severely ill with COVID-19. The health system had to restructure to manage the load, and elective surgeries were canceled and stayed canceled for 3 months while we collectively pivoted primarily towards managing the pandemic.

The research that I had done in the past primarily involved large dataset outcome studies for patients with brain aneurysms or acute ischemic stroke. We had a small team of very capable persons who were adept in curating electronic data from electronic health records. At the beginning of March, many of the early reports were coming in of COVID patients suffering major strokes and other neurologic symptoms. In the middle of March, with a large portion of my usual clinical activity suddenly restricted, we jumped into action designing a retrospective-prospective observational cohort study to try to identify which COVID patients were at risk for developing neurologic manifestations. In order to properly conduct this research, our group needed information on all COVID-19 patients presenting to our health care network.

We were one of the first research groups in our system to submit an IRB protocol, and thankfully through the major healthcare restructuring, the IRB stayed open. At the time, our local IRB had given utmost priority to COVID-19 related studies. These submissions were given immediate attention and the turnaround time on approval was quite rapid, particularly as it pertained to non-interventional observational studies. The rapidity of our approval gave us a head start and access to invaluable resources within our data warehouse group, which was able to ping us all the patients we were investigating with COVID-19. Probably about a week or two after starting, access to this data became restricted as nearly every research group in the system was having similar ideas. There were also growing institutional concerns about the public health message they were trying to portray, layered with the fear that outcomes in certain areas of New York City appeared worse than others. No one wanted to be considered the system that was doing a bad job managing the pandemic or their patients.

In tandem, it became apparent that many other clinician researchers wanted access to similar information. A counterpart in the Department of Neurology and I teamed up to create a research network of interested researchers who wanted to have access to information on COVID-19 patients. We were able to use Microsoft Teams as a centralized hub to help create networks of research groups for parties with similarly aligned research interests while also preventing overlapping research ideas. We could assign roles within specific projects and defuse any potential squabbles about authorship. As researchers expressed interest, we were able to easily addend our IRB to add additional team members with nearly same-day feedback. By the end of the project, there were over 50 researchers involved with various observational projects with clinician researchers looking at a variety of topics including COVID and ischemic stroke, COVID and hemorrhagic stroke, COVID and epilepsy, COVID and encephalopathy, COVID and race/ethnicity, and COVID and neuromuscular disease. While Teams was the hub for our centralized research machine, it was important to keep it maintained and protected and to ensure no patient information was placed in the group. This, in addition to managing the projects and making sure everyone who wanted

to be involved was included, became a large part of my job during the months of April and May. We used RedCap to maintain the protected patient information in a database and monitored access to it to ensure compliance. The effort to maintain compliance could not have been done well without the invaluable work from our research team, including our research coordinator and research nurse.

During this time, the IRB deftly maneuvered and created new action items within the IRB submission process. These action items highlighted the specific needs related to COVID research in order to speed up the approval process. The only major institutional challenge we faced was when it came time to potentially collaborate with other institutions; the policies regarding data sharing when it came to COVID-19 patients were very restrictive initially. It took quite some time to arrange data user agreements in order to be able to look at these issues within a larger patient population.

I believe that, during the worst months of the pandemic, it was likely very hard for the IRB to ensure compliance for researchers actually conducting research. Despite these difficulties, maintaining an active IRB throughout the pandemic to support research endeavors was an essential part of understanding more about this illness. For our group, these endeavors ended up in many manuscript publications that likely improved our understanding of the disease.

Interestingly, however, research outside of COVID-19 did take a back seat. One clinical trial we were beginning to start up right before the pandemic began had to halt. This delay in enrollment lasted 3 months. The clinical research arena suffered, as did the clinical arena. Many patients with diseases not related to COVID-19 suffered as a consequence of this pandemic.

While the pandemic clearly did more harm than good, there were some important lessons learned through it. For one, the idea of in-person informed consent became a serious challenge as hospitals restricted visitors for a portion of the time. Transitioning to a remote world for clinical care and research will likely be invaluable, particularly in our arena of neurologic disease. Many stroke trials involve patients that lack capacity and require a family member or health care proxy to enroll in studies. Finding these individuals when managing a condition like stroke, where every minute counts in order to save brain tissue, is a major challenge and barrier to enrollment in clinical trial research studies, particularly for disadvantaged groups, which often have complicated social structures.

Creating electronic applications for which e-consents can be performed and time stamped has the chance of increasing enrollment of patients with diverse social, racial, and ethnic backgrounds for whom in-person consent and enrollment may have previously been a barrier to inclusion. Of course, anything electronically driven comes with its own potential ethical risks as they pertain to data security and data permanence.

Sometimes it takes adversity in order to properly reassess the status quo. I am hopeful that through all of this, on the other end of the pandemic, it will be possible to conduct ethical research with less bias and increased accessibility.

COVID-19 Clinical Trials: A Voice From the Front Lines

Eric Lenze

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Getting Involved in COVID-19 Treatment Research

I am a clinical trialist because I believe that high-quality clinical trials save lives and improve health. They do this both by showing that new treatments are helpful and by determining that potential treatments are unhelpful and should

not be utilized. Both of these have occurred in the COVID-19 pandemic, due to clinical trial results (see https://pubmed.ncbi.nlm.nih.gov/32673060/ and https://pubmed.ncbi.nlm.nih.gov/32876694/) and by the fall of 2020, new COVID-19 patients were getting more effective care than COVID-19 patients had received in the spring of 2020.

By March 2020, it was clear that COVID-19 was a major public health problem, possibly the largest and most urgent in our generation. Moreover, there was no proven treatment for it. Both policymakers and medical researchers were proposing drug repurposing efforts to mitigate the negative effects of the illness. One good example of this is remdesivir, an anti-viral originally created to treat hepatitis C. There were, and still are, hundreds of potential candidates.

I lead a research team that conducts clinical trials for outpatients; for example, we recently repurposed an antidepressant medication to help age-related cognitive decline (See https://pubmed.ncbi.nlm.nih.gov/32212856/). So when my colleague Angela Reiersen approached me about an idea to repurpose the antidepressant drug fluvoxamine for early COVID-19 treatment, we decided to conduct a clinical trial.

The underlying idea was that fluvoxamine, a serotonin reuptake inhibitor, also activates the sigma-1 receptor. This receptor is involved in modulating the immune system, and a 2019 publication showed that fluvoxamine could prevent deterioration in sepsis by this mechanism (See https://pubmed.ncbi.nlm.nih.gov/30728287/). We hypothesized that fluvoxamine prescribed to COVID patients with mild symptoms early in their illness would prevent the clinical deterioration that is often seen around the second week of the illness due to an out-of-control immune response.

The Challenge to COVID-19 Research: We're All in This Together—Aren't We?

We first came up with the idea for the study in late March 2020, and by early April, we had created a study protocol and gotten it approved. The protocol called for a rigorous test of 15 days' treatment of fluvoxamine for individuals who recently became symptomatic with COVID-19 but were not yet seriously ill. We would test fluvoxamine against a placebo comparator, providing more high-quality evidence than can be obtained from observational studies (See https://jamanetwork.com/journals/jama/fullarticle/2773107). We actually recruited our first participant only 16 days after our first conversation about using fluvoxamine for COVID-19. This rapid onboarding was due to the efficiency of our university's COVID-19 committee, which set up a system for rapidly reviewing clinical studies, and our Institutional Review Board (IRB), which accelerated their review process.

But then came the main challenge: recruitment. This has always been the bane of clinical trials. We had the staffing to randomize six patients per day and manage them in the trial, and we thought that recruitment would be rapid, estimating it would take approximately 3 weeks to randomize 152 patients. In the end, it took more than 4 months.

Our recruitment challenges were a two-fold problem: regulation and apathy. Regarding regulation, our IRB governs only one hospital in our hospital system (which is only one system among many in the region). Thus, it proved impossible to recruit within the wider ecosystem of the numerous hospitals and COVID testing sites in the region. We had no way to contact SARS-CoV-2 positive patients unless they were part of our university's medical school or its affiliated hospital

We were also unable to get help from area organizations, who could have told patients about COVID-19 clinical trials but refused to do so. We were surprised by this because we thought there would be a community "esprit de corps," and the organizations would be interested in finding treatments that would diminish the virus's adverse effects and help everyone. Moreover, we were not asking for organizations to make much of an effort, such as recruiting and consenting (this is the most time-consuming and difficult task in clinical trials). Surprisingly to us, they were unwilling to participate even in terms of allowing us to post advertisements or to include a study flyer in their paperwork given to patients.

In some cases, my research team and I encountered hostility towards clinical trials. For example, when we approached the County health department, they stated they would not help and that it would be unethical for them to even tell patients about the existence of COVID clinical trials. They stated they would only tell patients about clinical trials if the patient brought it up first, even while acknowledging that this never happened. This decision, on their part, did not appear to be due to any departmental policy. They felt this was the most ethical position, but I wondered if their paternalism was ethical; after all, by not informing a patient of the opportunity to participate in a clinical trial for their condition, they were removing autonomy from that patient. Another example was at COVID-19 testing sites; in one encounter, they told us to keep lawn signs advertising for the study away from their site.

More often, the problem was apathy; "not my job" was the default. This was not universal, and a few providers not only expressed enthusiasm for the research but actually helped by referring patients. But it was far too few, compared to the providers who failed to inform their patients about the availability of clinical trials or even discouraged them from participating.

These two problems—fragmentation and apathy—exemplify the US health care system when it comes to research. Indeed, we don't have a health care *system* in this country, but rather a complicated patchwork of independent operators. This contrasts with the RECOVERY study in the UK, a large platform trial testing repurposed drugs for serious COVID-19. There, they were able to get the entire country's hospitals to work together on this large RCT, randomizing hundreds of patients daily. The Chief Medical Officers of England, Wales, Scotland and Northern Ireland, and the Medical Director of the National Health Service wrote to all doctors and encouraged participation in COVID-19 trials. Unsurprisingly, then, most of the early findings about COVID-19 treatment came out of the UK: the effectiveness of dexamethasone, and the lack of effectiveness both for hydroxychloroquine and for lopinavir-ritonavir, for reducing morbidity and mortality in patients with serious COVID-19 (See https://www.recoverytrial.net/).

Ethical Challenges in COVID-19 Research

Aside from recruitment challenges, three ethical challenges arose. The first was that our primary recruitment method involved "cold-calling" individuals who recently tested SARS-CoV-2 positive. This is a highly-successful recruitment technique that is often approved by university IRBs. But some individuals express discomfort about it, usually articulated as "If I were a patient and you called me out of the blue, I'm not sure I would like that." However, we did not see any concerns or complaints in our COVID-19 trial, despite screening over 1300 individuals and randomizing 152. This may be because our study focused on outpatients who are not gravely ill and not in a position of possibly limited decisional capacity. We also avoided individuals with dementia or in nursing homes or assisted living facilities.

The second ethical challenge was how to manage patients in our trial. Since they had COVID-19 and were self-quarantined, there was no face-to-face contact. Instead, all aspects of the study had to be conducted remotely. We resolved this by emphasizing a high-touch approach whereby participants were e-consented via the phone and REDCap. Then study supplies (including medication) were delivered to their house, whereby they began participation. We checked on them frequently during the study with phone calls, supplementing the primary source of data collection for outcomes and adverse events, which was a REDCap survey. Another fully-remote trial for COVID-19 outpatients, which tested hydroxychloroquine (and found it ineffective), used a low-touch approach that was almost entirely automated and had a similar experience (see https://pubmed.ncbi.nlm.nih.gov/32673060/). So I would conclude that fully-remote trials with no face-to-face contact can be conducted safely and ethically, at least when the drug being tested is amenable to this technique.

A third interesting ethical issue was that we initially excluded pregnant women, but we were

approached by maternal-fetal medicine doctors who urged us to reconsider this position. There is a controversy about excluding pregnant women from clinical trials and whether doing so creates a disparity. It hadn't occurred to us that excluding pregnant women might be unethical. However, the Coalition to Advance Maternal Therapeutics, a consortium of about 20 organizations (such as the American Academy for Pediatrics), actually sent a letter to the directors of NIH and FDA, calling for the inclusion of pregnant and lactating women in COVID-19 clinical trials. As a result, we decided to include pregnant women. However, ultimately none participated in our study. Nevertheless, this experience calls into question the assumptions that researchers (and IRB reviewers) often make about excluding "vulnerable" individuals; there may be advocates for those same individuals who strongly feel it is unethical to exclude them without good reason.

Recommendations

There needs to be more cooperation in the US to support and advocate clinical trials. For that to happen, two things should change.

First, the federal government could clarify that one and only one IRB can and will govern a research study no matter where in the US it is conducted, whether it is at one hospital or in every hospital in all 50 states (and 14 territories), including within the VA system. This is a simple, long-overdue change. I cannot overstate the amount of unnecessary bureaucracy and idiosyncratic decision-making (all of which impede progress towards new treatments and increase the cost of testing them) that could be swept away with the stroke of a pen.

Second, there needs to be a cultural change in our country's default position in providing medical care, which is anti-clinical research (with a few exceptions, such as cancer care). Leaders in health care at all levels could make this change by stating clearly that clinical trial participation is the standard of care for medicine. Hospitals and providers that refuse to tell their patients about clinical trials, or actively prevent patients from participation, are not providing the standard of care for treatment. Instead, providers could point their patients to clinicaltrials.gov (or even look on the site on their behalf); and, they could give an unbiased opinion about whether their patient should participate.

As a clinician, I can help people with treatment only because those treatments were demonstrated effective in clinical trials. Perhaps medical training needs to instill this way of thinking. Perhaps payers should reimburse providers for the time they spend assisting patients in learning about and deciding about participating in trials. Policymakers have the sticks and carrots needed to change behavior at the provider level. Of course, ultimately, it should be the patient's decision.

In the end, our trial succeeded. In August 2020— ve months after Dr. Reiersen rst contacted me with the idea—we unblinded our results and found none of the 80 uvoxamine-randomized COVID-19 had deteriorated, vs. 6 of the 72 placebo patients (see https://jamanetwork.com/journals/jama/fullarticle/2773108). This exciting but preliminary nding led to a larger, con rmatory trial, which is just starting at the time of this writing, in December 2020. Still, I can't help thinking we would have nished already if the US system was geared towards helping rather than impeding clinical trials. And the new trial may be a failure because of some of the problems described in this article that make clinical trials unnecessarily inef cient and challenging to conduct. It is my view that the changes I've recommended would make clinical trials faster, less expensive, and more likely to succeed.

Related Work.

Lenze, E. J., Mattar, C., Zorumski, C. F., Stevens, A., Schweiger, J., Nicol, G. E., . . . Reiersen, A. M. (2020). Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA, 324*(22), 2292–2300. doi:10.1001/jama.2020.22760

We'll Deal With That Later

Lauren T. Southerland, Jennifer A. Frey & Russell Williams

The office was empty and all the plants were dead. And while it is not atypical to find plants struggling for life in my personal office, it is not normal to find them in everyone's offices. It was mid-April and we had been in quarantine for COVID-19 and working from home for over a month. Initially, I had been better about nipping into my office to get supplies and things I needed, but once I had permission to take my work desktop home, my bedroom became my primary research space. I hadn't realized until I walked back in that day in April that four weeks had passed of doing all our work from home and no one had been in to water the plants. Even the cactus was drooping and brown. My research team and I had been working on starting up an interventional study to try to reduce COVID-19 infections in healthcare workers, and we were meeting in person to put the final pieces in place. My research manager Jennifer Frey and I needed to process map every element of the study, from where we would meet with potential participants to where we would draw samples and swab nasal passages. Hopefully clinical research would be easier to resurrect than the wilted cacti and dried-up spider plants. On a whim I decided to take every plant I could find home with me to see what could be saved.

For everyone in the world the pandemic has been dif cult. For an emergency medicine physician who also does clinical research and just took on the leadership role of Director of Clinical Research for the Department, it was very dif cult. Add in navigating remote schooling for 4 kids, including a 3 year old boy who is part-tornado, and work challenges were now work-life tournaments with both sides competing ferociously over every minute of time I had. The kids quickly adapted and developed shrewd attack plans: sneaking into the bedroom of ce to try to make crazy faces during work Zoom calls or nabbing my cell phone so I couldn't double-secure login to hospital websites. Even with my amazing husband at home full time, trying to sort through the 7 websites, (which means 21 different logins between the 3 school age kids) and guring out how to upload things like "paragraph uency readings" and kindergarten art projects, it was hard. I can't imagine how unmanageable it was for single parents. Who knows if they were learning anything. *We'll worry about the gap in their education later. . . .*

When COVID hit, we had a team of paid undergrad students, clinical research assistants, research coordinators, and managers recruiting and running 11 different studies in the Emergency Department. In late March, all non-critical research was halted and employees were sent to work from home. We scrambled to find encrypted, HIPAA compliant laptops for everyone. We had several studies that required follow up phone calls to participants. The team figu ed out how to use the hospital operator service to mirror calls so patient participants only saw the hospital number and not their personal cell phones when they called from home. Jen ordered headsets for the team off Amazon. *We'll figu e out reimbursement later . . .*

Our studies ranged from the management of septic shock to identifying delirium in older patients to urine microbiomes. All those were halted as being non-critical and we quickly pivoted to starting up several COVID trials. *We'll worry about the consequences to our other studies later . . .*

This was my first interventional drug trial. An interventional drug trial typically takes 12–18 months of work to ensure that all the appropriate regulations, permissions, and operating procedures are in place. We had to condense that down to 4–6 weeks. You could almost hear the echoing screech as the entire research mechanism at this large academic hospital switched gears to the all-COVID setting. The number of committee decisions, permissions, and signed contracts was amazing. It was lots of late nights, early mornings, and learning on the fl . The first week of June we enrolled our first participants. Between the extra clinical shifts in the Emergency Department due to call offs from COVID infections and the extra hours put in to get the study up and running, I was as wilted as the 15 rescued office

plants on my kitchen table, trying to remember what water felt like. *I'll gure out how to sleep later. . . .*

Each step was a mountain. Everything needed approval, and everything had to be adapted to COVID-19. Our lab did not have approval to process potential COVID samples so we had to contract with a cardiologist whose lab was certified until we could get ours up and running. That involved a new biosafety hood and new protocols. We had to figu e out where to do the COVID testing, because nasal swabbing is an aerosole-generating procedure that could spray viral particles around the room. How do we keep research staff safe? We decided to do recruitment and testing in an old ambulance entrance that had an overhang, so we could be outside with good air flo . We didn't know at the time whether COVID-19 was transmissible on objects, so we had to figu e out how to safely package, label, and ship samples. We took signed paper consents, bagged them in gallon-sized plastic zipper bags, wiped them down with disinfectants and then let them sit for 2 weeks in the hope that any virus would be dead by then. What about ordering gift cards for participants? We decided to email amazon gift cards instead to avoid touch transmission. But university finances was (perhaps appropriately) concerned with us asking for hundreds of dollars in Amazon gift card numbers and we had to go through multiple layers of approvals. We ending up starting the trial without them and emailing participants their gift cards 4–6 weeks later. Everything had to be single person use and disinfected or thrown out. *We'll worry about climate change and the environment later . . .*

The university attempted to centralize some research, but there was so much and often it was unclear who had the authority invested in them to approve a protocol or study. We had to write our own guidelines for how to keep our employees safe. And as a research director, how do you choose who gets to work from home and who has to come in at 5:30 in the morning and be at greater risk of COVID exposure? We had so little knowledge of how this virus worked in the first few months. Who needed to be protected? The staff member with the newborn baby or the one with comorbidities? We ended up discussing it as a group and letting people volunteer to come back in person vs work from home. *Is there a way to make it fair? We'll figu e it out later . . .*

Research budgets didn't account for the extra costs of cleaning supplies and PPE. Luckily, our hospital had early access to an N95 mask recycling program so we were able to get masks for our research team. I had a huge box of plastic eye glasses leftover from my kids Nerf gun birthday party a year ago, so I brought in dozens of extra eye protection. But were we still safe? The study involved investigating prophylactic antiviral medication to try to prevent the transmission of COVID to healthcare workers. But how did I prevent transmission to my research team? Every time someone had a sore throat, malaise, headache, fever or cough they had to call off work and quarantine. You couldn't shrug off any small symptom in yourself or your family members, because you don't want this to be the time that the headache is COVID and you infect all your work colleagues. No one wants to be Typhoid Mary (or would it be COVID Karen?). The stress levels were amazing. We were trying to do the same load of work with 70% of our staff working from home. I'm just grateful our Department Chair was committed to retaining all our staff and not furloughing or fi - ing anyone. *We'll figu e out the budget deficits later. . . .*

Over the months all the new changes became routine. Slowly, more staff were allowed back on campus to help out. But we were always short of people and tall on work to be done. We still can't allow any of our student research team members any contact with patients or patient samples. The hiring freeze put into place due to COVID budget short falls has crippled us as well. In clinical research, we typically lose several team members each spring as they get accepted to medical school, nursing school, residency or other programs. We had three staff members leave us for these reasons but could not fill their positions. Everyone is trying so hard, and I wish I could give them all a bonus or a month's vacation. But where would they go? *We'll deal with staff burnout later . . .*

At least when you come to work now you get to hang out with all the office plants, returned to their owners with greener leaves and new, bigger pots.

It is October now and the cactus just bloomed. It's lopsided and has some new weird purplish cactus pads, but it bloomed. We've figu ed out recruitment procedures, lab processing, office social distancing, e-consenting, and how to order in takeout and then eat it in separate rooms. COVID levels are rising again our state, over 5,000 new infections a day. I feel like we have just figu ed a lot of this out and hit our stride in clinical research and now I'm worried we will have to shut down and do this all over again. At least if that happens, I'll know to take the plants home too. *And we will figu e the rest out later.*

Practice-Based Primary Care Clinical Research During the COVID Pandemic

Barbara P Yawn

Acknowledgments. Thank you to the investigators, research staff and Practice Based Research Network (PBRN) staff and practices in the CAPTURE trial.

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All clinical research became challenging early in 2020 with the first surge of the SARS-CoV-2 (COVID) pandemic. All multi-centered academic clinical trials faced many challenges. Our study based not in academic centers or practices, but in primary care practice-based research networks (PBRNs) seemed to have added layers of challenges to identify, understand, and overcome.

Our project enrolled primary care practices and then patients directly in their primary care practices for a single in-person visit. Before COVID, the clinical staff of the practices were invited to a lunch session that provided a 45-minute online review of the clinical topic. Patient participants completed the questionnaires and spirometry and peak flow testing required for this study at the time of their visit to their primary care office for another reason. 12-month follow up was done with an online, telephone or mailed patient survey, and from review of the past 12 months of health care use from participant's medical record abstraction and designed to be completed in about 50% of participants.

Beginning in early March 2020, the practice sites and all of our practice-based research networks halted all research. Over the next few months, the sites allowed some COVID-related research to begin or resume. Our study did not fi that category. Over the summer months of 2020, some other studies that could be accomplished via virtual interactions like telephone or online surveys were allowed to restart. We did not meet that standard either since we need spirometry and peak flow testing

Most of our work had to be refocused from completing enrollment to identifying safety protocols and procedures for the consent and questionnaires. The spirometry and peak flow procedures, which were considered a nebulizing procedure, were a very large concern in the summer of 2020. The primary care clinics saw them as potentially viral spreading procedures.

We were working with six PBRNs spread around the country with different periods of "surge" and very different oversight of practice-based primary care research. In some PBRNs, the requirements for safety were set by the PBRN's affiliated academic medical center. For other PBRNs, requirements were set, or also set, by regional health care systems. All practices needed to work with the local practices to understand their concerns, educate them on levels of risk, and address safety needs unique to that site.

Obtaining personal protective equipment (PPE) was difficult since our study was not being completed in the hospital setting and was often not directly associated with an academic medical center. Once we obtained PPE through the AMA, SGIM, and AAFP programs, we needed to work on "fit testing" for the N95 masks, which is not readily available at all primary care practices or PBRNs (e.g., those based in rural areas). We needed to develop "cleaning and re-use" policies that fit with the academic and CDC guidance but were realistic for our broad spectrum of sites.

One approach that appeared to be acceptable to several primary care practices and research oversight groups was to offer visits virtually. While virtual enrollment and visit completion would have been a nice solution, our academic pulmonology investigators and the experts on our DSMB did not feel that at home pre- and post-bronchodilator spirometry could be done with sufficient accuracy to meet the needs of our study. So, we developed the concept of "mixed" research visits—part virtual and part in person. Virtual visits, however, required a change in consenting to online or e-consent.

For many sites, the use of e-consent was a barrier requiring new formats, new tools, and in some cases, extensive work with local IRBs to approve not only specific e-consent tools but also garner support for the *concept* of e-consent, even for our minimal risk study. IRBs expressed concerns that potential participants would not understand or be engaged in the e-consent process as they are in "face-to-face" consents. We overcame this by providing support across PBRNs with IRB talking points, e-consent examples/templates, and embedded questions within the e-consents assessing potential participants' understanding of the e-consent.

By the last quarter of 2020, experts appeared to become more comfortable with safety protocols for spirometry testing that included PPE for the coordinators doing the testing (e.g., N-95 masks, gowns, gloves, face shields), cleaning of the rooms with appropriate products, use of HEPA filter during and after the procedure and letting the room sit idle for 30 minutes after the testing. This allowed the go-ahead for our study in some sites.

But the process of allowing a patient to enter a primary care office became a new barrier. For some practices and PBRNs, the patient simply had to report no possible COVID symptoms and not have a fever (>99 F) on the day of the visit. Other sites required a negative "COVID test" within 48 hours before the visit. However, the COVID tests were not always available, and getting results back in 48 hours was often not feasible. While the study agreed to pay for these required tests, getting the billing system established to direct the charge to the study, rather than the patient or their insurance, was complicated. At times, it appeared insurmountable for primary care sites and health systems that were not academic medical centers and used to such studies billing for tests.

The next barrier was the education session for the staff at the enrolled primary care clinics. No longer could the staff meet in a lunch room, since in most clinics, the "lunch" or conference room was not large enough to accommodate social distancing for a staff meeting. Using the videotaped educational sessions for the primary care clinicians, we devised an online completion program by individuals similar to other online CME programs. This is not as efficient and often misses the inclusion of non-clinician practice staff but currently appears to be the best compromise.

Our study coordinators required regular updating and reassurances that their safety and the safety of participants, as well as others working in or attending those primary care practices, were a greater priority than completing the study. Fortunately, we had already established excellent working relationships with our PBRN staff and the coordinators. We provided them with educational programs about COVID safety and prevention, supported by the best available evidence and tailored to this project. The PBRN study coordinators were supportive and instrumental in working through creative ways to facilitate restarting enrollment using virtual and in-person visits, recruitment from telehealth visits, and education of potential participants related to their safety.

We had to redo our consent forms not just to accommodate the e-consent format but to include information on protecting participants from study-related spread of COVID and to accommodate mixed virtual and in-person visits.

Since our study has respiratory endpoints, it was also necessary to add a section of questions related to patient-identified possible COVID infections and queries about symptoms, testing, and hospitalizations. Additionally, we added questions about COVID immunization, either as part of a study or as part of the roll-out of widespread COVID immunizations. This required IRB review but also

several other steps in our follow-up processes and programming.

The cost of our study increased significantly but we were unable to obtain any additional funds from the Federal funding agency. Fortunately, our study team has excellent ongoing relationships with several large pharmaceutical firms. With the blessing and assurance of meeting all Federal requirements, we were able to obtain supplemental industry funding from 6 industry partners.

Just as most of our barriers appeared to have solutions, the fall and winter surge of COVID happened. Two sites that had been able to restart have had to slow down recruiting at the request of the primary care practices. One PBRN has been told that all primary care research is suspended again until late in the first quarter of 2021 due to the need for all attention to be focused on COVID-related care. Two PBRNs have had to give up future recruiting. One site in a large California city has had several of the practices they work with go out of business or go bankrupt. These practices cared for insured individuals and homeless people but have not been able to find continued funding for staff and unable to enact telehealth. The other PBRN could not keep coordinators employed during the extended "lay off" of enrollment due to COVID. We have onboarded a new PBRN who plans to begin enrollment in late December 2020 but is located in a region that has experienced a recent "COVID surge." The impact of this is not yet clear.

Like all clinical researchers, we have struggled to update, modify, and adapt our implementation plans to fit our research partners' many needs, especially the PBRNs and primary care practices and the potential patients. Our research question is not any less important now than before the pandemic—it's just more difficult to complete the study and obtain an answer.

Related Work.

Yawn, B. P., Han, M., Make, B. M., Mannino, D., Brown, R. W., Meldrum, C., . . . Martinez, F. J. (2021). Protocol summary of the COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) Validation in Primary Care study. *Chronic Obstr Pulm Dis, 8*(1). doi:10.15326/jcopdf.2020.0155

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What's a Hospital to Do? Equipoise, Pandemics and Single-site Clinical Trials

Todd B. Seto

Acknowledgment. Dr. Seto would like to acknowledge the support and collaborative work of his colleagues at The Queen's Medical Center.

I learned a lot about clinical trials over the past year. Some things were unexpected, and challenged the validity and feasibility of implementing research during a pandemic. Some things were anticipated, based on long-standing differences in philosophies of care and the bureaucracy of research regulations. Some things were reaffirming, and reminded me of the importance of scientific discourse and how much I enjoy my job and working with my colleagues.

I learned the most during the spring, when initial reports of potential COVID-19 therapies were largely observational and poorly designed. We tried—and failed—to join multi-center clinical trials that were forming to study new therapies. Rather than waiting, we designed and ran our own single-center randomized clinical trials, basing our protocol on recommendations from the WHO and anticipating that we could eventually contribute our data to larger collaborative efforts and meta-analyses. Our first studies were randomized controlled trials of hydroxychloroquine (NCT04345692) and tocilizumab (NCT04412772) for hospitalized patients with COVID-19 that started on March 26, 2020 and June 2, 2020 respectively.

The most unexpected lesson should have been better anticipated. Equipoise does not mean the same thing to all people, particularly among

physicians who highly value autonomy and in the midst of the anxiety and uncertainty of a growing pandemic. For some of us, clinical equipoise—when there is professional disagreement among the community of expert practitioners as to the preferred treatment—was sufficient to justify enrolling patients into randomized clinical trials. For others, it was not. Rather, individual equipoise—when a health care provider is uncertain as to the preferred treatment—was the standard. Seemingly entrenched on the extremes of two sides, it was hard for our clinicians to find common ground. Thus, discussions on the merits of hydroxychloroquine quickly shifted to disagreement on the role of physician autonomy vis-à-vis the broader professional community, the meaning of "evidence-based," the obligations of physicians to their patients, and the ethics of randomized controlled trials during pandemics.

Recognizing the importance of open discussion and transparency, we convened a COVID-19 therapeutics advisory group, with broad representation by front-line clinicians, pharmacy and research staff. Although the group was unable to reconcile the tension between clinical and individual equipoise, there was still broad support for the clinical trials as long as access to the study drugs were not restricted to study participants. Interestingly, nearly all study eligible patients were ultimately offered the opportunity to participate in our studies.

The most anticipated lesson I learned was both the most frustrating and satisfying. As we started our clinical trials, it was apparent that the bureaucracy of research regulation and compliance, built over decades to minimize institutional risk and maximize human subjects protection, was poorly suited to match the rapidly evolving clinical milieu of the early pandemic. As the COVID-19 community incidence steadily increased and the hospitalization rate started to rise, we knew that waiting months for IRB approval and weeks for Medicare Coverage Analyses (MCA) and financial start-up would be too slow. Also, it was a shock when we were reminded that our institution, as the sponsor of this single-center study, had to pay for the cost of the study drugs—manageable for hydroxychloroquine but less so for tocilizumab, particularly without external funding support or the ability to bill insurance. Scientifically and fiscally responsible, it seemed as if we were being "punished" for doing the right thing—offering these medications as part of a randomized controlled trial rather than usual care. However, we were fortunate to have institutional support to pursue our studies. Our hospital IRB committee held ad hoc meetings to help expedite our study reviews; our MCAs were prioritized and completed within 48 hours; our hospital leadership agreed to internally fund all study-related costs; and it took 7 days to go from conceptualizing our hydroxychloroquine study to enrolling our first patient. It was rewarding to see our research administrative team recognize its role in our institution's response to COVID-19.

On a larger scale and looking back over the past year, I learned two more things. First, it should be easier for clinical sites to participate in large multi-center clinical trials, particularly during the early stages of a pandemic when the evidence base for effective therapies is thin and the need for rapid action is a priority. Broadening the range of study sites would likely increase the diversity of study participants, improve the engagement of under-represented communities, and increase the generalizability of study results. If an expanded, diverse network of clinical trial sites across the country is not feasible, then a central repository with detailed study "start-up" information—protocol, case report forms, informed consent templates, centralized IRB agreements—would help smaller sites stand up studies that would be similar to one another methodologically and increase the likelihood of high quality meta-analyses or systematic reviews when reviewed in aggregate. It did not make sense for us to run a clinical trial in isolation, but we were unsuccessful in joining a multi-center trial and we did not want to wait. What would we do while we wait? How long would we need to wait? Therefore, we proceeded with our studies, basing our protocol on the standard WHO template and our inclusion/exclusion criteria and treatment regimen on the published literature. We fondly described our studies as "Lego" pieces that would hopefully be

"picked up" and connected with other studies as part of a larger meta-analysis. We are pleased that our plans worked out. And now, nearly a year into the pandemic, we are participating in several large, multi-center clinical trials. But I think that we could have done better.

Second, it is somewhat enlightening, and slightly embarrassing, that our early clinical trials were more valuable and impactful to us—my institution, my colleagues—than to the larger scientific community. Does the world need another single-site, underpowered clinical trial? Is the importance of a clinical trial only in the data that are generated? We mulled over these questions and agreed that there is more. Many of us found value in "carrying on" in the midst of uncertainty and unease. We found that our clinical trials had a galvanizing effect—they built a common cause for our providers to rally around; they provided a sense of order and purpose; they reaffirmed our identity as scientists contributing knowledge to the larger community. I know that this description seems overstated, but it is not; although it is arguably small-minded and frivolous from the outside looking in.

It has been an interesting year.

Teaming up with the IRB: The Power of Collaboration

Rebecca Erwin Wells

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Conflicts of Interest None

Trial registration: clinicaltrials.gov (NCT04319445)

The question kept nagging inside my head, "How can I best help others?" When the pandemic began, I was overwhelmed with a deep desire to serve. I became a physician to help others, and here I was, at the onset of this international health crisis, working on analyzing results from my prior clinical research projects and caring for my patients with headache, but not directly on the frontlines caring for COVID-19 patients. Schools had just been shut down at the state level, and local quarantine orders were advising working from home as much as possible. As I was contemplating my next steps, I went into my office early on Sunday, March 15th to bring home essential supplies so that I could conduct my research from home. Although the parking lot was nearly deserted, I recognized the familiar cars of several senior administrators. I envisioned them meeting behind closed doors to discuss our hospital's pandemic strategies. With my degree in public health, I considered searching for the room where they were meeting to charge in and volunteer my services. I imagined being greeted with joy and gratitude at the assistance I was offering. I quickly realized my vision of aiding could be viewed as barging in un-invited on a senior-level meeting, obtrusively interrupting important planning. I opted to defer that option. Rather, I recognized I needed to fi d concrete opportunities to use my expertise to help in specific ways

Later that day, I emailed an Italian colleague and friend. As headache physicians and mindfulness researchers, we had bonded at a scienti c meeting in 2019. I reached out to check on her given the dire circumstances in Italy, and she explained how she had started offering online mindfulness classes through "Mindfulness for Milan," to support the public in managing the stress and anxiety during

the lockdown. A light bulb went off inside my head. As a trained mindfulness instructor, I could offer mindfulness to my patients. The emotional toll of the pandemic was overwhelming, and I was especially concerned about my patients with migraine, as stress can be a common migraine trigger. Inspired by my Italian friend and colleague, I decided to begin leading my patients in online mindfulness sessions. Further, as a clinician researcher, I also wanted to know if these sessions were of value, and if so, would participants want additional sessions?

I felt an urgent need to provide this help as rapidly as possible. When this pandemic began, it felt like the crisis would only last a few weeks, and I wanted to ensure this service was available promptly. So many were suffering, and this plan was a palpable way I could use my expertise to support others. Although the idea arose in wanting to serve my patients with migraine, I quickly realized that it did not need to be exclusive to migraine and could benefit anyone inte ested.

I began working on the IRB protocol and the plan of action. Given the need for social distancing, I wanted the entire study to be conducted online and remotely, so patients could feel safe participating in the comfort and safety of their own homes. I had recently conducted a study with an online educational session for patients, and had embedded REDCap surveys before and after the online session to capture pre/post data. Although initially I thought I would lead the mindfulness sessions live-online, I realized that having the session prerecorded would allow pre- and post-surveys to be completed online, similar to my prior study and ideal for capturing immediate pre- and post-session responses.

As my plan unfolded, a multitude of questions began to emerge on how to conduct the study in the most ethical way possible. For example, without any in-person contact but with an active intervention, what was the best way to obtain informed consent? Further, with the entire study conducted remotely, could I share the information broadly with colleagues at other institutions so that they could share this offering with their patients as well, or would they need an IRB in place as well? Since the study was online, could I advertise nationally, and possibly even internationally? Could anyone interested participate, or did the study have to pertain to a clinical population? I did not even know the active state of our IRB, with everything shutting down in the midst of the quarantine. Moreover, if operational, would they be available for the rapid approval of this study that I was seeking?

The next day, Monday morning, March 16th, I reached out directly to our IRB director, a reliable and resourceful leader whom I had come to know over the last 8 years at my institution as someone always ready to offer assistance. I wanted to ensure full clarity with these nuanced questions from the onset to ensure a smooth IRB process and rapid approval. I received an immediate response that the IRB office was open, operational, and studies related to COVID-19 were receiving top priority. I received swift responses to all my questions, with specific recommendations and concrete advice. For example, as long as other providers at other institutions were just acting as referral agents, they would not need a separate IRB. The informed consent form would be online prior to the pre-survey, and they helped me draft a full consent with all the appropriate language, but concise enough to be effective in an online environment. I could define eligibility as anyone interested in participating in the mindfulness session, without any exclusion criteria. I could recruit internationally. As I worked through the online IRB submission process, I encountered several additional challenges, and with each issue, I received prompt support. Although no one was working in their hospital offices, our IRB officers communicated rapidly via email and provided home office numbers for availability. As I was finalizing it, I was told they were anticipating my submission. Such efficient responses and anticipation made me feel like we were working on the same team, side-by-side, all of us together versus the sideline clock ticking.

By that Thursday, March 19th, my initial submission was complete and it was in the hands of those at the IRB. At most institutions, for a full

protocol initial IRB review, I would be expecting at least a 2-week turnaround. However, for this study, I received the first round of feedback by Friday, March 20th. Given the oncoming weekend, I reached out that Friday afternoon and spoke with the IRB director himself over the phone to clarify further issues. One of the challenges was that the study needed to be registered on clinicaltrials.gov prior to IRB approval. Our institution had recently instituted a new program to support investigators with this registration process, and someone had already started this process for our study! I communicated directly with this kind and supportive person, even speaking on the phone over the weekend, to comply with this protocol. By Saturday, March 21st, our study had received expedited IRB approval.

I was filled with joy and amazement! My research study had moved from a floating idea in my head to IRB approval and study implementation within 7 days—what would be astonishing during normal times, and nearly heroic in the midst of a pandemic. While the world was "shutting down," our IRB was gearing up. I felt like our research was valued, my goal for rapid turnaround understood, and my voice appreciated. I was able to communicate directly with the IRB team and received speedy responses to all inquiries. Further, the awareness of the need for COVID research and its priority at our institution created an environment that allowed for a multitude of important COVID projects to be initiated and conducted.

The IRB was originally created to protect patients in the midst of horrific unethical research practices. Unfortunately, over the years, many researchers have often felt like IRBs can hinder research. Slow responses, delays in providing feedback, and a multitude of forms and amendments can sometimes feel like dramatic administrative burden to the successful conduct of research. Conducting this research study in the midst of the pandemic gave me a newfound respect for our IRB team. The entire experience made me feel like we were working side-by-side, with the same goals in mind. Our IRB's approach was to ensure that our study was conducted with the highest ethical rigor in a transparent and seamless fashion, providing support along the way to facilitate its success.

We found very powerful and encouraging results from our now published study. (See Farris et al. in the related works.) Our goal had been to recruit 200 participants, and we surpassed our goal with 233, including 20 international participants. We were able to target patients with migraine, but also overworked health care workers and the general public. We found significant improvements in momentary stress, anxiety, and COVID-19 concern from our single mindfulness session, and most participants wanted more sessions. Given the study was inspired by a colleague helping others, we asked participants what they were doing to help others, and were overwhelmed with the positive responses of acts of kindness.

Garnered with this information, I proceeded to lead 13 weekly mindfulness sessions over the summer, and received positive feedback of its value in people's lives during a time of such uncertainty. The pandemic has been an overwhelmingly stressful time, and we wanted to provide a program to target the emotional well-being during this crisis. In the process, we also discovered that the pandemic has created an enhanced sense of altruism. Having the support of our IRB during this time created a smooth and efficient process that aided the success of our research. Using my skillset and expertise to serve others through clinical research in the midst of this pandemic has been extraordinarily meaningful and allowed me to respond to the question that so many have asked at this time of crisis, "How can I best help others?"

Related Works

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Editor's Note. This story complements Brian Moore's story, which is included among the IRB professionals' stories in this symposium.

Reflections on Conducting Research From Home During COVID-19

Laleh E. Coté

Acknowledgments. Special thanks to the many students, faculty, and professionals who have shared their personal experiences or offered to assist with recruitment for this work. I extend my deepest condolences for the many lives lost as a result of COVID-19, and for the hardships that many are faced with during this difficult time. In the last year, this line of work has greatly benefitted from the contributions and strong support from Anne Baranger, Colette Flood, Julio Jaramillo, Jenna Nicolas, Gia Jones, Seth Van Doren, Sinéad Griffin, Katelyn Cooper, Carrie Des Roches, Dianna Bolt, Megan Hochstrasser, Hope Henderson, Yulia Golubovskaya, Clarice de Azevedo Souza, Melanie Leavitt Cantarutti, Kristy Nordahl, Jennifer Doudna, and Brad Ringeisen. Thanks to Erin Dolan (UGA) and Jennifer Collins (USF) for sharing insights from your work on similar projects.

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The very first email I received that mentioned the novel coronavirus disease 2019 was on February 14, 2020. Valentine's Day. In a newsletter summarizing science highlights, a few short sentences announced the name of this new virus that had infected thousands of people as "COVID-19," and the fact that experts had yet to find a good method for its diagnosis. The second email about COVID-19 that I received was from work on February 25; it explained that the spread of the virus was likely to impact international travel. It provided information from the Centers for Disease Control and recommendations to wash hands and use hand sanitizer to prevent its spread. There was no mention of wearing masks yet. In the subsequent weeks, I heard from more organizations and groups I'm affiliated with about the emergence of this disease and speculation from each group about the seriousness of the situation. For many people at that point, it was something too strange or too worrying to think about. But for me, this disease led to an entirely new line of research.

Back in 2007, the first real laboratory I stepped foot in as a community college intern focused on using microbiological methods to answer questions about ecosystems. It was with that group that I learned to hold a pipette, stitched my iPod Classic into my very own lab coat, and foolishly printed a typo-filled research poster without letting my mentor (a postdoctoral fellow) review it first. Now, 14 years later, it feels important to have been introduced to the world of science and research through microbiology. Reading articles about how PCR is used to detect the presence of COVID-19 after a nasal swab brings back powerful memories of working in the lab, concentrating on moving tiny amounts of liquid from one well to another, sometimes for hours on end. I have since transitioned from working in biology laboratories to working with undergraduates and graduate students, conducting research in the social sciences about the scientific community, and—as of this past year—about the scientific community's response to COVID-19.

One of the surprising things about conducting research related to COVID-19 is the speed at which everything happened. Like many people in my professional community, I had begun to work entirely from home in the spring, and had been notifie that my summer research plans to collect field data would need to be altered. I had to purchase a cooling

pad to rest my laptop on because it quickly became overheated from back-to-back virtual meetings during the day. I was filled with dread every time I read the news or opened my email inbox. I sent an email to my research advisor on March 26 about my first ideas for a national survey to poll students majoring in the sciences to find out how COVID-19 may have impacted their short-term academic or career plans. I pored over as many articles as I could on the subject, reading about school closures, challenges with distance learning, people juggling childcare and work at home, and loss of access to research laboratories and field sites. We quickly realized that it would be beneficial to expand the scope of this research to include students, faculty, and professionals who were all feeling the impacts of this crisis. By April 9 at 1:55 pm, we had our Human Subjects approval in hand, and received our first survey response by 3:46 pm the same day. With a bit of preliminary data analysis from the survey to inspire an expansion, I submitted several grant proposals for a second project by the end of April. This project was designed to study the impact of COVID-19 on science research experiences, which can be gateways to graduate school and scientifi careers for many students (Krim et al., 2019). By May 12, I had received news that one of these proposals was successful, which enabled me to organize some research assistants, update the IRB protocol, and proceed with recruiting subjects for the study.

In reflecting upon what I've learned since March, when I began redesigning my research to accommodate questions related to COVID-19, the firs thing that comes to mind is the emotional burden. It was difficult for me to begin working from home, especially when people in my "bubble" maintained jobs outside the home. I worried about the illness and death already caused by the virus, as well as the safety of my own friends and family. My child was in kindergarten at the time, and his school year effectively ended early when distance learning was clearly not working as planned. There were so many ways my life had been affected—far too many to name here—and many of them created huge amounts of anxiety and stress. So, in designing research to explore the effects of COVID-19 on a group of people, I was informed by my own experiences, perspectives from the people in my professional community, and a strong desire to contribute as part of a collective effort to better our society during this crisis. But, it hasn't been easy. I can't choose when my family has a rough week, when news will arrive of another person who has died, when one event creates a logistical bottleneck, or when we have to schedule nasal swab tests due to a run-of-the-mill cold or possible exposure. Being mostly confined to the home isn't conducive to writing or inspiration, and so it takes me a lot longer to produce something (anything!) than it normally would. And finall , because I am studying the impacts of COVID-19 while dealing with them myself, data analysis can be disheartening because it often reveals a truth that I expected to uncover: people are struggling. One survey response in particular has been burned into my mind, though it was only the first of many to give me pause. A university faculty member, to whom I am forever grateful for completing the survey, revealed that they are more afraid of dying than they have ever been before. If infected, the severity of the illness seemed unpredictable, and they were worried. I read this on my phone, and then just stopped and sobbed in the middle of my kitchen. In that moment, it was all just too much to handle. As more data came in, there have been a few similar moments since that time.

After COVID-19 began to spread around the world, scientists and researchers from many disciplines were interested in exploring ways to slow its spread, treat its symptoms, prevent deaths, or help with the healing process. I have come across at least 20 different surveys designed to investigate the effects of this pandemic on different aspects of respondents' lives, and I completed as many of them as I could. One in particular stands out in my mind, because I was so pleasantly surprised by the theme: how the owner-pet relationship has been impacted by COVID-19. My own dog has brought me a lot of peace since I began working from home, and it felt like a tribute to her to share this perspective. It felt good, almost cathartic, to answer the questions, and I took my time.

Unfortunately, I have had a difficult time responding to some other surveys, as they seem to have been written merely to obtain information,

without even a comment to acknowledge the pain a person might be feeling as they reflect on their life. These have felt too transactional, too cold. To be clear, I understand that not everyone has had the same lived experiences during this crisis. Many of the respondents to my own survey explained that they were privileged to have had only minor disruptions to their personal lives. However, even very preliminary information-gathering prior to designing a survey this year should have yielded some understanding that many people are in great distress. The emerging crisis was both a) highlighting great inequities in our society, and b) exacerbating those inequities for many people. This year, so many people have felt the cruel impacts of this crisis, with very little time to prepare for or process the situation. Even when asking for information, a gentle and flexible approach feels right regarding language, scheduling, and other logistical details that are so critical to conducting social sciences-based research.

Although the process between designing the survey and obtaining responses was quick, I spent many hours reading essays and news articles, as there was almost no social sciences-based research published at the time. Social media gave me a glimpse into the real-time perspectives of undergraduates and graduate students in the sciences. I made lists about the topics they most often raised, comparing these to comments made by faculty and scientists. I also shared my draft surveys with researchers in my network, and piloted the early drafts with undergraduates and peers, to make sure the language was easy to read, and would generate thoughtful responses. Finally, I read through all of the communication COVID-19 crisis I could get my hands on, and compared this with language posted on college, university, and company websites to think about what messaging the people in my study may have been exposed to previously. All of this was done to acquaint myself with my target audience, in terms of the situations they may have found themselves in, and to make a decision about what type of data resulting from this work would be most useful to the larger scientific community. This work required me to kiss my child goodnight and then stay up for a few more hours to focus while our home was finally silent. I don't recommend this way of working, but at the time, my sleep was often disturbed from stress, and I was finding a way to reconcile my desire to contribute with the understanding that my planned research projects were impossible and no longer relevant. I shuddered at the idea of simply moving forward with an interview in which we didn't address the elephant in the room; how could I interview a student in Summer 2020 to ask them about their career plans without first checking in on them to find out how COVID-19 may have affected their life? How could I claim to understand my study population without incorporating the larger context in which their experiences sit?

Beyond these initial ideas, I have found myself navigating many other circumstances related to this work. While recruiting, many people were supportive of these studies, but explained that there were already plans to survey their own community about their experiences. Others explained that they had too much else to deal with, or simply did not respond (not unusual for this type of research). With all of this, I have come to the conclusion that there is no single "right" way to conduct research during a global pandemic. Still, I try to find a respectful balance. On the one hand, this work—to find out what people are experiencing in order to share insights with decision makers and those within the communities represented—is valuable. *What are they going through? What are they thinking about? How could I best serve them by telling their stories?* On the other hand, I don't want to intrude on people during a difficult time; this esearch is intended to create a positive impact, after all. After the murder of George Floyd at the end of May, I stopped actively recruiting responses for the survey, because it seemed frivolous in comparison to the important discussions the nation was engaged in at that time. I am interested in the data, yes, but only because I am invested in the well-being and success of my target population. The delicate dance between pushing forward and holding back is one that I assume I will become only more familiar with as time passes. The work will change as society does.

Yes, this year has challenged me. Yes, this work has challenged me. And yes, I would embark on

this work again, because it is a way for me to make sense of the world around me, and to give a voice back to the people in my community.

Related Works

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Assessing Risk When Everyone's Afraid: The Challenge of Seeing Health Care Workers as People When Our Need for Them Is So Great

Rebecca C. Hendrickson

I was a second year resident when I witnessed, from across a hallway, a failed resuscitation of a child hit by a car. Her image on that table—looking so much like my own young daughter—and her mother's screams haunted me for many weeks. I couldn't understand why: "She wasn't even my patient!" I told my mother in disgust. I was just there. It seems strange to me now, but in the moment, my mother's response came as a shock: "You may be a doctor now, but you are still a human being who witnessed a child die." I was still early in my training, but already it had become a fixed, unquestioned belief: a physician is absolutely invested in the care they provide, but ordinary human emotions should no longer affect them.

The idea that traumas you experience as part of your job do not "count" is widespread. I think it is likely at the core of a number of the challenges I experienced as a researcher attempting to address the traumatic stressors experienced by health care workers and first responders working during the COVID-19 pandemic. I am a VA psychiatrist working in a PTSD specialty clinic, and I run a research program focused on understanding how particular combinations of chronic and acute traumatic stressors can lead to the long-term changes we associate with PTSD. I also study how to treat, and, hopefully, prevent these changes.

When the pandemic first hit New York City, I began to hear my friends and colleagues in medicine describe not just long, harrowing work shifts, but also insomnia, nightmares, intrusive memories of the horrors they were seeing, and a sense of always being on edge. Although these symptoms can't count as symptoms of "PTSD" until they have been present for more than one month, what we know so far of the pathophysiology of both acute stress symptoms and PTSD suggests the underlying mechanisms are fundamentally the same. If treatment is indicated earlier than one month after trauma, in practice, most of the medication options are the same as well. The biggest difference is that it's so hard to study acute stress disorder. Here, we are always using these treatments "off label," relying on what we know of PTSD treatment, pragmatic experience, and rare case series, rather than large, organized clinical trials.

This gap in evidence base is most frustrating in the area of long term outcomes. Our theoretical and preclinical models would suggest that treating acute stress symptoms with medications that block the noradrenaline response to stress, such as the common PTSD medication prazosin, will also decrease the likelihood of these symptoms becoming the chronic symptoms seen in PTSD. However, there is no good clinical evidence for or against this hypothesis.

When I began to hear all the symptoms of acute stress that were emerging from frontline clinicians working during the COVID-19 pandemic, the right research move seemed obvious and urgent: if we could treat frontline clinicians experiencing such symptoms with prazosin, we would be providing the best treatment option I know of to a population that needed immediate intervention. We would be generating the first structured clinical trial data to address the efficacy of this intervention for, in particular, the acute sleep-related symptoms of acute stress disorder. We would also provide the first direct test of whether treatment with bedtime

prazosin during or immediately after a traumatic stressor could decrease the risk of PTSD at 6 months. Although we would need to conduct the trial virtually to reduce the risk of COVID-19 transmission, we could do this using the same adaptations we were using in our clinical practices, which had rapidly converted to entirely virtual care. As the PI of a research team already running randomized clinical trials using the drug prazosin, this was a trial we could begin within weeks, with resources we had on hand. My team and I poured ourselves into the most rapid start-up of a trial we'd ever considered.

I had not expected the trial to be concerning to our IRB. I have always had a good working relationship with our IRB, who I have found to be thoughtful, conscientious, and committed to supporting quality research. My previous prazosin clinical trial, which was much more complicated, had been approved with thorough review but without issue. But the questions I received upon turning in the application immediately made it clear there was a problem. We were asked whether we could really justify having a placebo group if the need were as great as we indicated. We were also asked, moments later, how we could justify using an "experimental treatment" where there wasn't yet clear data to support its use in this specific context. The adaptations to virtual care that already felt standard in clinical practice were concerning in the research context. The intervention we were offering had been used safely and successfully in contexts ranging from active-duty soldiers to elderly Holocaust survivors residing in nursing homes. Every outcome we had measured had suggested that occupational functioning improved when prazosin was used to treat traumatic-stress related symptoms. Still, we were asked a large number of questions about whether our intervention posed a risk to the health care system overall. Could we add an evaluation of occupational functioning for each participant to ensure our treatment did not interfere with their work duties? Could we require permission from participants' employers before they were allowed to enroll?

These responses were unexpected to me. I felt blindsided and, to my surprise, almost personally hurt—although I didn't initially understand why. In parallel with this, however, the grant mechanism to which we were applying changed its RFA shortly before the deadline, removing its previous references to effects on health care workers and specifying that only work addressing mental health effects on patients would be considered. As I set aside our nearly completed and now worthless grant proposal, I understood why I felt so personally troubled: a theme throughout these decisions was that health care workers working during the pandemic were no longer being viewed as people, for whom the traumas they were experiencing could exert a real, personal toll, but instead as workers, whose human responses to trauma could be ignored.

After significant delays, the study was finally approved with severely limited inclusion/exclusion criteria, which were so narrow that we struggled for months to recruit anyone eligible for the intervention. However, we were able to recruit a substantial number of individuals into the observational portion of the study, consisting of longitudinal surveys assessing the experiences of health care workers and first responders—and the level of distress described, in rating scale and in free-text responses, was immense. Our data also suggested that the intensity of PTSD symptoms reported was not only strongly related to our index of COVID-19 related occupational stressors but that PTSD symptoms were also the overwhelming mediator of work-related functional impairment. With this result in hand, we reapplied to expand our enrollment criteria for the interventional portion of the study—and again, we were held up by the IRB out of concerns about the potential to negatively impact the work performance of health care workers during a pandemic.

I have struggled sometimes to understand how our IRB, which I know is working hard to make the best decisions it can, is seeing the situation so differently from how I am seeing it. I am reminded of a conflict that comes up from time to time when clinicians speak with statisticians about a potential clinical trial: the statistician will say, but this is an inadequate design—the right design requires three

times this enrollment. The clinician will say, but that is not possible—and some information is better than no information. The statistician will disagree: it is worse to think you know something you do not. The clinician will shake their head. Fundamentally, I see these types of disagreements as being related to one's role in the system. If you are a gatekeeper, it is in fact your job to be focused on the risks associated with potential actions—seeing any wrong step as more dangerous than staying in one place. But when you are a clinician, it looks different: you know that day after day, you make decisions with whatever imperfect information is available to you in that moment. If there is no RCT to guide you, you go with the open-label trial; if there is no open-label trial, you go with the small case series. Some data almost always seems better than no data if you are the one forced to see the consequences for individual patients every day. The risks of inaction weigh far more heavily when you are the one seeing the costs of the status quo or making decisions in real-time.

Similarly, when I page through the responses we have gotten from the now hundreds of participants, more than 75% of whom are reporting clinical-range symptoms of PTSD, depression, and/or anxiety, and few of whom report any current access to or utilization of effective treatment, the cost of inaction feels very high. Every deferral by the IRB—to take more time to make a careful decision, to seek input from the ethics board—comes, for me, with the grief of thinking through the cost of more weeks of failing to provide any intervention for these individuals who are my colleagues, more weeks of failing to have publishable information for the community at large to use to address this emerging crisis in our field. In contrast, the IRB, sitting much further removed from the personal stories of those affected by the decisions, maintains a different framework for risk assessment: the risks associated with action are the focus, and the risks of inaction are not.

I wish to be very clear: I believe this difference in perspective is not only necessary, but also a significant part of the purpose of the IRB process. With anything as high stakes as the delicate ethical balance of clinical trials research, we all require those less immersed in the immediacy of our own work to review our ideas and provide an outsider's check on our determination to answer the urgent-feeling questions before us, to act when we see suffering. I am grateful for the dedication of our IRB members in playing this critical role.

Exactly how this balance in perspectives plays out, however, can be challenging to calibrate—and proved particularly so in the context of the COVID-19 pandemic. Here, again, I wonder if we are misled by our belief—perhaps hope—that we are somehow shielded from the influence of human emotions in our professional lives. The increased level of fear the COVID-19 pandemic brought to each of us may have affected us in different ways depending on our position, but I suspect that my sense of intense urgency to act as I witnessed the suffering of my colleagues was paralleled by a similarly intense fear of being the one to allow significant harm, via risk to our health care system during a moment of crisis, for those within the IRB who felt charged with this role. For each of us, the ability to step back and see our most immediate concerns as part of a larger set of risks and benefits, and to discuss our perspectives effectively with those who had a different view, became more and more challenging the more intense the anxiety about the impact of the pandemic became for all of us.

The impact of fear on our assessments of risk and how we make decisions is part of being human and an important way we protect ourselves against mistakes in high-risk situations. However, it is a mistake to ignore or deny these impacts—to pretend any of us are immune to them. Even as we sought to study the impacts of COVID-19 related stressors on others' work, we were feeling them, too.

Related Works

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Reflections on Conducting Pediatric Mental Health Research as a Result of the COVID-19 Pandemic

Patrick W. Romani

The deadly disease caused by the novel coronavirus (SARS-CoV-2), better known as COVID-19, has produced a public health crisis around the world. Public health orders have been issued at various times throughout the pandemic to control community spread of COVID-19. These orders have ranged from highly restrictive stay-at-home orders to slightly less restrictive orders that limited the number of people dining in a restaurant. In response to these orders, many workplaces transitioned to remote work, and schools and daycares temporarily closed, thus requiring students to engage in virtual education. This meant that working families used to working and having their children receive education or care outside of the home suddenly needed to cope with the reality of needing to complete all of these activities together, under the same roof. Feelings of isolation and stress with managing demands of being a parent, educator, and professional have led to the untoward side effect of a mental health crisis pandemic.

At a time when mental health research was perhaps most important, universities placed significan restrictions on research practices. These restrictions included limiting in-person contact between research teams and participants and funding agencies instituting temporary freezes on distribution of research funds. Thus, researchers needed to modify protocols to maintain productivity during this challenging period when they may also have been asked to be parents and educators for their children. My research protocols involved evaluating medicine-behavior interactions among children diagnosed with autism spectrum disorder (ASD) and delivering in-person trainings to school teams throughout the state of Colorado.

With a young son, now at home full-time and a wife who also worked in the healthcare field, these projects would have been adversely affected if the University had not already shut them down. While highly disappointing and stressful, I used this situation to leverage my experience both conducting research and using technology to deliver mental health services to maintain research productivity.

First, over the years, I had many interactions with the Institutional Review Board. During this time, reviewers became familiar with the types of projects I typically put forward for review and they had given me valuable feedback on how to format applications appropriately. Second, the advice a previous mentor had once given me took on new meaning. He told me that an effective psychologist should participate in 100% clinical activities and 100% research activities. That is, all clinical work should be done in a manner that can undergo a peer-review process and be published. I believe this mindset was important when considering the rest of my experience conducting research during the COVID-19 pandemic.

While I have personally heard the saying, "these are unprecedented times," in reference to the challenges presented by the pandemic, this awful situation has led to unprecedented creativity and strength. I became connected with a multidisciplinary group of pediatric mental healthcare professionals in a collaborative manner to meet the ever-growing mental health needs of children and adolescents. We were particularly proud of our development and execution of partial hospitalization programs (PHP) via telehealth. These incredible clinical efforts deserved to be rigorously studied to (a) document these creative and innovative services and (b) ensure effective clinical care was being delivered to a population of children that sorely needed it.

An obvious area for investigation was evaluating the clinical outcomes of these programs. To my knowledge, the delivery of PHP services via telehealth had not been completed. Many hospital settings were charged with creating them, though. We worked to adapt our data monitoring procedures to track child progress with virtual PHP services. In one example, we used previously published research to guide procedures to coach parents of children diagnosed with intellectual or developmental disabilities (IDD) while conducting behavioral assessment and treatment procedures. The IDD PHP program delivered therapeutic services for 3.5 hours per day (a half-day PHP program). A behavior technician coached parents remotely to conduct behavioral therapy with their child while supervised by a psychologist and board-certified behavior analyst. Additionally, a social worker and psychiatrist met with the patients multiple times per week to identify after-care services and an effective medication regimen, respectively. The average reduction in child problem behavior from admission to discharge was 87.0% following a virtual PHP program. The previous two years' data from this PHP documented an average reduction in problem behavior of 87.5%. Thus, the virtual services were approximately equivalent to the in-person treatment.

While these results were encouraging, providers and families reported concerns. For example, families reported that their children would refuse to log into the virtual therapy sessions or that they struggled to balance work and be present for their child's therapy to ensure participation. Providers reported similar concerns. Anecdotally, providers expressed concern about their ability to coach patients and families using a virtual platform they had not previously been trained to use. Many healthcare providers (e.g., psychologists, social workers, psychiatrists) were not trained to deliver telehealth services in graduate school. Following approval from the IRB, my research team sent acceptability surveys to all providers in the PHPs delivering care and the children and families receiving this care via e-mail.

We had 44 providers and 19 children/caregivers enroll in the study. Overall, participants recommended having at least a portion of therapeutic visits occur in person before transitioning to telehealth visits. Additionally, the preferred length of telehealth visits was approximately 1 hour, which was consistent between providers and children/caregivers.

While the aim of much of my research activities changed as a result of the COVID-19 pandemic, they were nonetheless important and fulfilling. Studies using medical providers or children/families experiencing a mental health crisis are vulnerable populations, particularly during a pandemic. Thus, the informed consent process was highly important to us when we could not physically see participants face-to-face. We ultimately received approval to use a post-card consent form. Since our project evaluated child, family, and provider perception of the telehealth services being delivered, the risks were minimal. This allowed our research team to avoid in-person encounters to document consent to participate. In addition to being able to use an electronic consent document, I believe our endeavors were successful because the surveys were accessed by participants remotely. My co-investigators and I could meet, develop the surveys, and execute the project at home, at night, or on weekends, whichever was most convenient. While conducting survey-based research was not any of our typical research procedures, we were able to adapt to our environment and find success. Third, I believe our research endeavors were successful because of the numerous interactions I had with the IRB prior to the pandemic. During the pandemic, IRB committees reported being overburdened by the number of pandemic-related research studies sent for review. This led to a slow-down in reviews. However, because IRB reviewers were familiar with the types of research protocols I usually put forward for review and have given me ample feedback on formatting applications, this application quickly moved through the institutional review process. Rapid reviews were important to my co-investigators and me because of the time-sensitive nature of the projects. Clinical activities truly did change on a daily basis. Thus, to conduct the evaluations described above, we needed to have the IRB applications approved quickly. We made it clear in the cover letters that this research was to evaluate the effect of the pandemic on pediatric mental

healthcare services. This, along with the previously discussed relationships, led to these successes. I would heavily encourage researchers to connect with their IRBs early and often to ensure understanding of preferred formatting characteristics of applications and to communicate idiosyncrasies of applications to ensure rapid review.

The COVID-19 pandemic has produced disruption around the world. Researchers were also affected by sometimes having their protocols abruptly stopped or needing to learn how to balance being a parent, educator, and researcher at the same time. A team of us modified our traditional research studies to continue evaluating important clinical outcomes for a high-need population of children. While this is a once in a lifetime experience (hopefully!), I believe there are activities every investigator can consider to improve their flexibility and skills to interact with the many stakeholders responsible for conducting a successful research study.

Remote Research Hinders Recruitment of a Diverse Sample

Beth Prusaczyk

Funding. This work was funded by the Institute for Public Health, Washington University in St. Louis

When the pandemic began, many researchers sought to capture the historical event from the perspectives of different groups of people. As someone who conducts research related to older adults, I knew the pandemic was a matter of life and death for them. Along with my colleagues, I wanted to understand the pandemic's impact on older adults from a "whole-person" perspective. We wanted to know how older adults' health and mental health were affected and what they saw as the positives to come out of the pandemic, and how the pandemic fit within the other events in their lives or lifetime. Therefore, we began a study for this purpose and designed it, knowing it would have to be conducted during the pandemic. We did not have to transition a pre-existing study into this new environment and were able to plan for an entirely remote operation. For their part, the IRB reviewed and approved the study quickly, though we purposefully chose not to collect Protected Health Information (PHI) so that our study would not have some of the required restrictions and protocols necessary when collecting PHI. We had conducted studies online or over the phone before, but we were still not prepared for some of the challenges we faced.

From the beginning, we decided to make a concerted effort to recruit older adults who were low-income, Black or African-American, or identified as LGBTQ. We wanted to ensure our sample did not represent only more privileged older adults who were likely to navigate (and literally survive) the pandemic better than these other groups. However, our intentions to recruit a diverse sample were met with significant logistical challenges as we attempted to conduct a fully remote study during the pandemic. First, we knew we would be using an online survey since there was no way we could have in-person study visits at this time. An online survey would be the easiest and most efficient way to reach a large number of older adults. Second, we also wanted to compensate our participants for their time but what would normally be trivial tasks for an academic research shop—the purchasing of gift cards, printing letters, addressing and stamping envelopes, and putting them in the bulk mail—became impossible in the pandemic. Therefore, we decided we would send e-gift cards to the participants' email addresses. However, both the online survey and e-gift cards would require the older adult to have Internet access, have the proficiency to navigate the online survey, and use email; things not every older adult may have, especially those who are low-income. Fully virtual/remote research, whether done out of convenience or necessity, brings with it a significant cost to recruiting and enrolling diverse populations who are often excluded from research to begin with.

For participants who did not wish to take the survey online, we offered them the option to complete the survey over the phone with a research assistant. However, again in normal times, the

research assistant would call from their desk phone at the university and leave that call-back number on the person's voicemail. Now, our research assistants were all working from home, all over the country, with phone numbers representing those different areas. Many participants would not answer calls from numbers they did not recognize or that were outside of the area. Furthermore, we did not want the research assistants to have to expose their personal cell phone numbers for the study, but if they blocked their number when making calls, participants would understandably not answer a blocked number either. If the call went to voicemail, we had the research assistants leave my offic number as the call-back number. Of course, I was also working from home and was then having to regularly check my voicemail and try to quickly relay returned calls to the research assistants so they could try the participant again. It wasn't until very late in the study that we set up the voicemail-to-email system, where you receive an email with an audio recording of any voicemails you receive. This allows me to forward that email to the research assistants and saves time and it is unfortunate that we didn't know this was an option until we were nearly done with recruitment. Overall, our system was inefficient and frustrating for the research team and participants alike and I'm sure our recruitment suffered because of this.

Lastly, we learned a painful but valuable lesson very quickly when our community partners posted our recruitment flyer on their social media accounts. Apparently, in a virtual world, scammers and bots search social media for posts containing words such as "gift card" and then flood the online survey with fake responses in an attempt to receive the gift cards. Within hours of one of our community partners posting our flyer on their Facebook page, our online survey was bombarded with nearly a hundred responses, all very clearly from bots, many from overseas. Luckily, we were able to quickly spot this happening, shut down the survey, and remove the fake responses from the data. However, this meant we could not have the online survey link posted anywhere on social media, which significantly hindered our recruitment efforts. Now, if an older adult were interested in participating in the study, they would have to email or call us to express interest, and we would then send them the link. We thought this inconvenience was the end of the scammers and bots but we subsequently learned that, even if you remove the survey link from the flye , a flyer just mentioning gift card compensation for an online survey will still be flagged by scammers on social media and the email address on that flyer will be bombarded with hundreds of emails from bots posing (poorly) as older adults begging—pleading—for the survey link so they can receive the gift cards. Thankfully, we had set up a study-specific email address and were not using one of the study team members' individual email addresses so the hundreds of messages were at least contained to the study-specific inbox where they were flagged as spam and deleted. But yet again, this meant we could not even mention on our flyer that we were providing compensation if we wanted that flyer to be posted on social media. In the end, we decided to avoid all promotion on social media so that we could still include the gift card information on the flyers that our community partners circulated privately to their clients or organizations but this meant we were not able to recruit as many older adults as we wanted.

Overall, our commitment to recruiting a diverse sample and compensating participants for their time and effort made the logistics of recruitment, conducting the survey, and remuneration extremely challenging. While I am proud of the sample we ultimately recruited, I am sure that had we been able to recruit more widely, we would have ended up with a larger and more diverse sample and without this our results are not telling the full story of how the pandemic has impacted older adults.

Houston We Have a Problem: Ground Zero for the US Coronavirus Outbreak

Yuan-Po Tu

Acknowledgments. This work could not have been possible without the culture, spirit and resilience

of The Everett Clinic community. Thank you to the lab who handled thousands of trial specimens; Epic who wrote and rewrote the code when protocol changes were made; my colleagues in the walk-in clinic who covered for my absence, and especially the all the nurses, medical assistants, and personal service representatives for their dedication in taking care of our patients.

Funding. Funding for the SARS-CoV-2 assays was from a generous donation by Quest Diagnostics.

Friday, February 28th, 2020, 4:15 PM—Houston We Have a Problem

I looked at my messages and noticed I had missed a call from the county's health district epidemiologist. I wondered what she was calling about but wasn't too worried. As the contact person for infectious disease at our clinic, it was not unusual for me to receive communication from the health department. When she answered the phone, I jokingly asked her what she had to report late on a Friday. What she said next changed our world: two days previously, a patient in our clinic had tested positive for coronavirus (COVID-19).

As I listened, gathering the details, I frantically looked up the case. I typed a message furiously to my chief medical officer

> Houston we have a problem.
>
> One of our patients tested positive for COVID-19.
>
> I am on the phone getting the details.
>
> Press conference at 7:00 PM.

Reviewing the chart, I saw that the patient was a local high school student who had presented to one of our clinics two days earlier. He had a high fever and a rash. The patient had not traveled outside the country. In our electronic medical record (EMR) system, the screening algorithm identified the patient as potentially infectious. He had been appropriately triaged and placed in a room with a mask on. The providers taking care of him documented that they wore appropriate personal protective equipment. So far, so good.

Washington State—Ground Zero for the US Coronavirus Outbreak

Six weeks before I got this call, the first person hospitalized due to COVID-19 had occurred at a hospital in town. Now reacting to the first community-acquired case of COVID-19, The Everett Clinic opened its command center at 6:30 AM on Saturday, February 29. As it was a weekend, the focus was on containment. Initial operations focused on developing an urgent care strategy, placing greeters at all clinic entrances, and supply chain assessment.

From our previous experience with the 2009 H1N1 pandemic, we knew that diagnostics and supply chain management would be challenging. Our immediate concern was our supply of N-95 respirator masks. I led the clinic's response during H1N1, so we had a plan. Post H1N1, in the after-action review, we created a disaster response depot in our warehouse. Included in this were plastic barrier gowns and N-95 respirators. The Director of Materials Management instructed her team to place orders for more N-95 respirators and surgical masks immediately. We hoped the orders placed over the weekend would be in the front of the queue before the distributors were inundated with orders on Monday. We were relieved after the Director and I drove to the warehouse, pulled three pallets, and located our stash of N-95 respirators. Our relief was short-lived.

Monday, March 2nd—the Command Center

I was seated next to the Director of Materials Management in the incident command center when she informed me that over 10,000 surgical masks had been issued over the weekend. At the current utilization (burn) rate, we would soon have a critical shortage. In the 12 months preceding the pandemic, the clinic used 360,000 surgical masks, at a burn rate of approximately 1,000 per day. We projected that we would need 100,000 surgical masks per month at a burn rate of 3,333 masks per day. This estimate was very accurate—we have used 1.5 million surgical masks in the 12 months since the beginning of the pandemic. Mask supplies were the tip of the

iceberg—we faced multiple shortages throughout the pandemic.

The First Week's Response

The Everett Clinic was as well prepared to face the challenges of a pandemic as any organization. Our leadership was stable. Many of us had been part of the H1N1 response. We had cultivated close relationships with the Washington Department of Health (DOH), participating in the influenza monitoring program and submitting influenza specimens to the DOH for years. After the first case of coronavirus was hospitalized in our town in January, we hosted pandemic table-top exercises in conjunction with the Snohomish Health District. During the first weekend, I fielded requests from the DOH epidemiologist to obtain samples from children for COVID-19 screening. We suspected that COVID-19 was circulating in our community as our urgent care clinics were facing huge demands for testing from patients with respiratory virus symptoms who were testing negative for influenza. At the time, for a specimen to be tested for SARS-CoV-2, the person had to have been in Wuhan, China. The extent of the virus's spread would soon become apparent as the pandemic made a dramatic and deadly appearance at a nursing home and hospital in a neighboring community in March.

Designing the Experiment

With the mask shortages and arrival of COVID-19 in our community, it became apparent that shortages of N-95 respirators, collection kits, nasopharyngeal swabs, viral transport media and testing would be an on-going issue. The focus quickly shifted as we felt the impact of COVID-19 on clinical operations. During the first ten days of the pandemic, only the State DOH lab was able to perform SARS-CoV-2 testing.

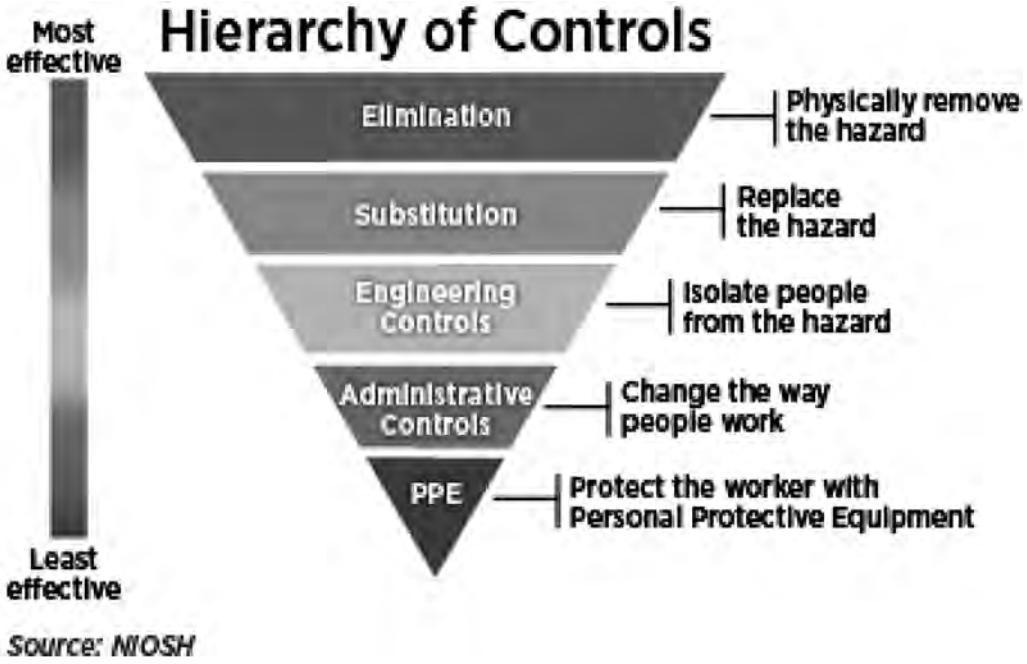
In January 2020, I had been awarded a clinical scholar fellowship by the Research and Development (R & D) arm of United HealthGroup. Using the Hierarchy of Controls, I began designing and planning a study to look at alternative ways to collect SARS-CoV-2 test samples that could potentially obviate the need for full PPE, thereby saving PPE and decreasing the aerosol exposure risk to health care workers. The virology lab at the nearby reference lab was just beginning to offer molecular testing for the diagnosis of COVID-19. Arrangements were made with the lab to perform the analytical testing for the proposed study.

The plan was to recruit 500 to 550 symptomatic patients presenting to our urgent care clinics. Each study patient would have four samples sent to the lab for analysis. We planned to capture essential elements of patients' clinical history and exam fin - ings in the EMR. The study design was to compare health care worker-obtained nasopharyngeal (NP) samples with patient-collected samples. Each study patient would have a NP swab collected by a health care worker then patient self-collected bilateral mid turbinate, anterior nasal and tongue samples. I partnered with a reference virology lab to perform the SARS-CoV-2 assays. Working closely with the EMR team and the R & D team of UnitedHealth Group, we designed the experiment, obtained an expedited IRB approval, and programed the EMR in ten days.

Serendipity—Saturday, March 14, 2020

On Saturday afternoon, I received a call from the R & D team of UnitedHealth Group informing me that they heard rumors that the Gates Foundation was attempting to run a similar study. The Foundation was excited to hear about our plans as they had been trying to set up a similar study to test the same hypothesis. I invited them to join our nal Webex call before starting the study the next day.

The Saturday evening call was the final check-in before starting the study. Leadership, lead nurses, urgent care clinical staff, representatives from the lab, and the EMR programmers were on the call, with the R & D team of UnitedHealth Group and members of the Gates Foundation listening in. I was reviewing the protocol and going over the details of the study when my phone rang. The call was from



the reference virology lab. In the past three days, the lab had received a larger than expected number of clinical samples and experienced longer turn-around times. The testing demand was not unique to the reference lab but was being seen throughout the United States. The lab director apologized and informed me that the lab could not keep its commitment to analyze the samples coming from our study. Without a lab to run the SARS-CoV-2 assays, the study was dead in the water.

What transpired during the next few hours on Saturday evening was amazing. After multiple contacts and calls, Quest Diagnostics agreed to perform the SARS-CoV-2 assays from our proposed study. We spent Sunday updating the institutional review board (IRB), rewriting the protocols and reprograming the EMR. There was only a day and a half delay with the reference lab pulling out of the study. By Monday, we were rolling out the protocol and training the sites one by one.

500 Study Subjects in One Week

At the beginning of the pandemic, the demand for testing was high, but few labs had validated assays, so access to testing was limited. Since our study offered an option for COVID-19 testing, enrollment was robust.

Recruitment occurred in multiple urgent care clinics. The samples were shipped to California where the SARS-CoV-2 assays were performed. Slowly, results trickled in. There were four samples per subject and the samples were subject to the vagaries of shipping to California. Once received, the results of the SARS-CoV-2 assays were compiled in a spreadsheet. As soon as the data was validated, it was sent to the UnitedHealth Group R & D team in Minnesota for statistical analysis. It took only a week before we reached 30 positive subjects on March 22nd.

Sunday, March 23rd—Presenting to the FDA

The online meeting with the FDA was scheduled for Sunday evening. We worked on our presentation right up to the 7:30 PM PT start time. As the principal investigator, I represented the study site. There were also members from the R & D team and the Gates Foundation on the call. The presentation went smoothly, with only a few questions asking

for clarification of our laboratory results. Many of the questions were regarding the patients' clinical appearance and ndings. As Washington State was the center of the United States' initial COVID-19 outbreak, there was limited experience in the presentation of COVID-19 patients in the outpatient setting. I noted that influenza-like-illness was not entirely accurate description of patients presenting in the outpatient setting. I noted that in our experience, many patients did not have elevated temperatures when they presented to the clinic and that their symptoms were more diffuse and variable than the typical influenza patient

Our Clinic Was Built for This Moment

It was only the third week of the pandemic. I was immensely proud of our organization's accomplishment in proving that patients could self-collect a nasal sample. The method was much more comfortable for the patient, safer for health care workers, alleviated the shortage of nasopharyngeal swabs, and a faster way to collect specimens.

I am often asked how we accomplished this in the middle of a pandemic in such a short timeframe. In many ways, we were fortunate (and unfortunate) to be the site where the first COVID-19 patient was hospitalized, and the first outpatient community-acquired case of COVID-19 landed. Our clinic values people and has the right culture to respond to a situation as unique as a novel pandemic virus.

Our collaboration in 2009 with the Health District and other community health care entities led to an unified county-wide vaccination campaign, in which 29,000 H1N1 vaccinations were administered in a single day. In the H1N1 action report, we created a disaster supply depot storing PPE in our warehouse.

The clinic has fostered relationships with the public health department through which we conducted table-top exercises on a pandemic respiratory virus in January 2020. I served on the State of Washington Disaster Medical Advisory Board to the State of Washington Secretary of Health. The EMR systems and the degree of standardization of our urgent care facilities have allowed for programming the protocol so that every enrolled patient's information was recorded in a flowsheet and could be extracted electronically. It was fortuitous that I was a clinical research fellow of the United HealthGroup R & D division.

I cannot say enough positive things about our leadership. They understood that we were in the eye of the storm and recognized that this was indeed a pandemic before the WHO officially declared COVD-19 a pandemic on March 11th. Our urgent funding requests for supplies and personnel were rapidly approved outside of the standard review process. After the reference laboratory pulled out of the study at the 11th hour, Quest Diagnostics stepped in and generously performed thousands of SARS-CoV-2 assays. The experimental plans were designed, executed and completed in a three short weeks in large part due to streamlined contracts, legal agreements, and expedited compliance oversight.

When I reflected on what we accomplished, I am filled with awe and gratitude for my clinic colleagues and their contributions. They are truly the heroes.

Related Works

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Caring for Others, but What About Us?

Francisco José Barbosa Camacho

Acknowledgement. I would like to thank all physicians, nurses, and health personnel who are fightin against COVID-19. A special thanks to the Biomedical Research Unit 02 and the Mexican Institute of Social Security staff for all their work and efforts

to understand the impact of this pandemic on our hospital personnel. And to my love, who brought the best of me during the most difficult times

The medical community often stands in a chaotic place. We are acclaimed by relieved patients or despised by their loved ones in cases where no effort was enough for saving their family member. A pandemic represents a similar situation. In some cases, it has brought us together as a species, taking care of each other and catching up with our relatives and friends; at the same time it has brought us apart when political or personal quarrels arise in the light of misinformation and quarantine desperation. With new papers and data as a sword and personal protective equipment as a shield, hospital and medical personnel have been the front-line warriors against this invisible foe. We as researchers, since the beginning, have been fighting along them to provide updated and new information to tackle the situation at hand.

Personally, I have always thought that patient's mental and physical health is as important as the medical and hospital personnel's. Lately, research has been focused on finding new diagnoses or treatment options, often ignoring the mental baggage this period has accumulated in the medical community. Additional to the usual stressors suffered by the medical personnel—such as long-hour shifts and heavy workloads—the fear of contagion, aggression from the general population, and an even bigger workload in hospitals can contribute to elevated levels of burnout. We focused our efforts in exploring the impact on the mental health of our city's hospitals' staff, especially the intensity of fear and anxiety in the COVID-19 and non-COVID-19 exclusive hospitals, as those hospitals attend to the biggest part of our general population. As only a few studies have been made regarding our caretaker section of the population, we sought to find how our hospital personnel were coping through this difficult time. In our research, we found that the general population often showed higher fear levels than those found in hospital personnel. As expected, the nursing and medical staff presented higher levels of fear than other medical staff members. We hypothesized that this could be due to a better understanding of the disease in terms of contagion mechanisms. Also, when analyzing the anxiety produced by this new disease, we found that at least 10% of our sample presented dysfunctional levels of anxiety. Between the fear of being sick and the anxiety created due to treating COVID-19 patients, a mental health crisis is rising within the front-lines of attention.

Another under-studied area this year is the effect of the pandemic on the students' mental health and academic performance. We surveyed over six hundred university students to analyze the effects of the quarantine confinement and online classes on their academic performance. It is interesting to fin that more than half the population has increased anxiety and depression when compared to their mental state before March. Those patients with increased scores of depression presented lower self-confidence in their academic performance and showed a lot less effort toward the program. I have heard colleagues' comments such as "they do not have anything else to do besides studying, why are they having such a hard time?" I sighed at the lack of empathy towards the emotional situation the students all around the world are facing: not only the struggle for survival and avoiding contagion, but additionally the impact of social isolation, confinement, and non-online friendly programs. These factors result in a distress-cocktail that will inevitably impact our students' professional performance and overall life quality.

In my opinion, the most vital recommendation I can give to fellow researchers who would like to perform studies during a pandemic is to keep themselves and their team safe. When one is excited to start a new project, one can lose track of basic protective measures. It is important to ensure physical and mental health before getting into a pandemic's research. Also, another key recommendation is maintaining many communication paths in order to avoid information loss or misunderstandings. This process has not been easy for us, as communication and contact with other researchers and physicians remotely can be tricky. With staffing shortages and all personnel busier than usual, the recruitment process was guided primarily by the labor union personnel. It

was easier to survey all the hospital staff this way and allowed our team to focus on data management and analysis.

We did nd some bumps in the communications road. For example, I was appointed as the site administrator in an international study. Primarily, my job was to take care of data recollection and maintain good communication between the research's HQ and our local research team. All information was sent via email from the UK to Mexico's HQ. Afterward, it was sent to me and nally to the hospital sites where information was not safely brought to everyone more often than not. This resulted in some language or software problems, such as not understanding the instructions correctly or online form lling mistakes. However, 2020 showed us that there are many ways to communicate independently from our location, from emails to messaging apps such as *WhatsApp*. Eventually, this evolved to Zoom meetings, as some problems were not easy to convey via written form, resulting in a better understanding between the teams, ensuring successful teamwork, and collecting the necessary data for the study.

Another complication we found as researchers was the journals' peer-review process. As many journals commented, fewer numbers of reviewers are available to undertake the titanic work of reviewing an ever-increasing amount of research work. As of May, Science magazine estimated that approximately 23,000 new articles were published regarding the pandemic, with this number nearly doubling every 20 days. We understand that reviewers need a flexible schedule in order to provide a proper review and time to digest all the information presented to them. This situation eventually backfi ed on us researchers, increasing the overall time for peer-review and the inevitable delay of numerous papers. To this date, many of our manuscripts are still in the infamous "awaiting reviewer response" or "under review" status in some journals.

Fortunately, life has permitted me to be on both sides of the spectrum, being part of the writing and production of manuscripts, as well as reviewing new manuscripts and research protocols regarding the COVID-19 pandemic. As a reviewer, I have witnessed both altruism and desperation from researchers who are honestly working to increase our knowledge of the disease and those who are only searching for a "quick publication" with protocols lacking science or sense behind their good intentions. Similarly, many colleagues have been stung with the research bug and started getting interested in writing about their clinical and personal experiences during the pandemic. All in all, despite its ups and downs, it has been fun to face and uncover details about this new disease, as well as providing any new information about it to the community.

Related Works

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Development of a COVID-19 Patient Registry in Central Illinois

Carl Asche, Mohammad O. Almoujahed, Sharjeel Ahmad, Anthony Dwyer, & Sarah Stewart de Ramirez

Intro. The Central Illinois COVID-19 Registry is designed to study outcomes of patients residing in central Illinois who have been diagnosed with COVID-19. The registry is intended to be a

collaborative project between three healthcare systems serving the rural areas of central Illinois, and a County Department of Health and University both in central Illinois.

Development of a COVID-19 Patient Registry in Central Illinois

The objectives of this project were to build and implement a COVID-19 registry and use it to answer a number of clinical questions: to assess clinical outcomes of patients diagnosed with COVID-19 in rural areas; and to examine the specific risk factors of clinical outcomes among patients with COVID-19 in rural areas. Potential risk factors meriting examination included distance to care, local rates of co-morbid conditions, racial and ethnic disparities, and lack of access to tertiary care centers, available medical treatments, access to SARS-CoV-2 testing, and telehealth services.

The 2019 novel coronavirus disease (COVID-19) pandemic has had a widespread global distribution to all inhabited continents with the highest number reported thus far being in the United States (U.S.). As of June 23, 2021, the US had more than 33,000,000 con rmed cases, and almost 600,000 deaths according to the Centers for Disease Control and Prevention (CDC).

Treatment of 2019 novel coronavirus disease (COVID-19) during the ongoing pandemic presents unique challenges for rural health systems. These clinical challenges are pronounced in the rural health setting where there is traditionally a deficit in locally accessible tertiary care and subspecialty medicine. Understanding the particular risks that rural populations face during the COVID-19 pandemic is vital in ensuring that the quality of care can be optimized in this traditionally underserved community. Use of the electronic health record (EHR) can facilitate a rapid awareness of disease course, treatment history, and test results, allowing for providing important insights into studying the rural population.

In order to locate COVID-19 data efficiently in the EHR, we proposed to develop and implement the COVID-19 flowsheet registry. A variable sheet was devised by the study team capturing all the information we believe was needed to address the clinical questions that were posed. The database was intended to integrate data from the participating multiple institution EHRs to support patient care and act as a registry. In our proposal we specifically aimed to assess rural setting COVID-19 management and adherence to available guidelines such as those from the Infectious Diseases Society of America (IDSA) and Surviving Sepsis Campaign. They recommend giving most therapies under clinical trial. The only FDA approved antiviral medication for severe COVID-19 infections is remdesivir. That was granted emergency use authorization (EUA) on May 1, 2020 and was subsequently FDA approved on October 22, 2020. Our specific study aims were to assess the clinical outcomes of patients diagnosed with COVID-19 in rural area and to examine the specific risk factors of clinical outcomes among these patients.

COVID-19 has spread heavily in urban areas and its growth rates were found to be considerably higher in large cities due to high socioeconomic connectivity. Urban areas were seen as suffering from the shortage of medical resources and hospital beds. As a result, states with large urban populations demonstrated high confirmed cases and deaths.

However, rural communities have been affected as well from this pandemic although we don't have true prevalence in rural communities due to limitations in disease surveillance. The rural community generally lacks certain important aspects of medical care due to geographical constraints and resource limitations. In addition, the rural area is at risk largely due to having a larger elderly populations. Therefore, understanding the particular risks that the rural community faces for COVID-19 is very important in order to try to maximize effective medical care to this population.

Early detection of risk factors in rural populations is an urgent problem to prepare for as there are limited medical resources in rural communities. In order to identify risk factors in the rural community facing COVID-19, we will develop a COVID-19 patient registry by combining three healthcare systems serving the rural areas of central Illinois. Although the number of patients were relatively

smaller than in the urban areas, our registry data are highly representative of COVID-19 patients in rural communities.

Our study is unique and has the potential to identify risk factors in COVID-19 patients living in rural areas. Use of an up-to-date electronic registry of COVID-19 cases will help bring to light these unique risk factors.

To rigorously investigate health outcomes in the rural community during the COVID-19 pandemic, we will assess COVID-19 management in rural settings and measure adherence to national and international management guidelines. To achieve this, we will develop a COVID-19 patient data registry by combining the Electronic Health Record (EHR) of three healthcare systems in the local community. This data registry will represent a large proportion of COVID-19 patients in rural Central Illinois. Our aim was to conduct statistical analyses to identify risk factors on clinical outcomes among COVID-19 patients in rural area.

The COVID-19 registry team and outside collaborators felt it was important to not only build and implement the registry but to also use it to answer clinical questions. Adding to the literature about the need for disease speci c, easily viewable, and readily reportable EHR content could benefit clinicians and researchers locally, nationally, and globally in terms of answering questions to benefit the patient and the community.

In terms of research design, this is a registry of COVID-19 patients in a Midwestern region using electronic medical records from a multistate health system from January 2020 onwards. Our study methodology was constructed to compare clinical outcomes in the central Illinois area. Target patients would be those with a positive COVID-19 test. We planned to employ a specific statistical model based upon outcome variables to examine risk factors of clinical outcomes.

All patients who are positive from COVID-19 test will be included whether or not they are hospitalized, which means that patients who are home-isolated without hospital admission will be included. The registry data will include all clinical information on patients with positive COVID-19 from diagnosis to 30-day follow-up after hospital discharge.

In addition to clinical information on patients, we plan to collect demographics, socio-economic factors, and local area information as risk factors. Local area information will include distance to care, local rates of co-morbid conditions, racial/ethnic disparities, and lack of access to tertiary care centers, available medical treatments, access to SARS-CoV-2 testing, and telehealth services.

We plan to conduct statistical analyses on patients who are positive from COVID-19 test. Outcome variables include the number of COVID-19 patients per population, the hospitalization rate among total positive patients, mortality rate among positive patients and mortality rate among hospitalized patients. Our specific study aims are to compare clinical outcomes between the local more populated area and other areas in Illinois to examine whether there is any disparity in outcomes based on location. A key variable is an 8-category variable indicating the location of the hospital. All outcomes will be reported among 8 locations within Illinois State. Descriptive statistics will be collected on demographics, socio-economic factors, comorbidities, and local area risk factors among 8 locations. Another specific study aim will be to conduct statistical analyses to identify risk factors on clinical outcomes. For continuous outcome variables, we will employ generalized linear model with log link to examine risk factors. For binary outcome variables such as morality, we will employ logistic regression. Control variables will include demographics, socio-economic factors, comorbidities, and local area risk factors. Risk factors of interest include distance to care, local rates of co-morbid conditions, racial/ethnic disparities, and lack of access to tertiary care centers, available medical treatments, access to SARS-CoV-2 testing, and telehealth services.

In terms of specific inclusion criteria for subjects our study interest were as follows: patients with both medical and pharmacy eligibility during the patient identification period; patients with zip code information; all cases regardless of age, patients must be 12 years or older on index date (children

12–17 years and adults 18+ years); and patients who died

No identifying information for any patient will be published. This study will not affect patients' care or coverage. Thus, the primary risk to the patients and families is data loss, privacy concerns, or HIPAA violations. Raw data (including EHR) will be stored in a dedicated secure password-protected server provided by one of the three participating health care systems. According to the need in this study, relevant information will be extracted from the raw data. Only de-identified data will be shared with the team members for further analysis and modeling. Only de-identified summary data and the results of analysis will be reported publicly.

Adaptive and Pragmatic Approach to Clinical Research: The Silver Lining of a Global Pandemic

Emanuele Chisari & Javad Parvizi

In response to the evolving COVID-19 pandemic, most local and national governments and professional bodies endorsed the cancellation of elective surgery. This action was in an effort to free up hospital bed capacity for possible admission of COVID patients and to preserve supplies of personal protective equipment (PPE).

Our institution also experienced cancellation in elective orthopedic surgery for a few months in line with the strategy mentioned above. The adult reconstruction division, which performs over 5,000 hip and knee arthroplasty per year, came to a complete halt for a few months. During this time, numerous patients with disabling arthritis of the hip and knee had to endure hardship while waiting for openings of elective surgeries. As a complementary and essential activity, our institution's clinical research division also halted operations from March to July 2020. Employees in research were instructed to work from home while clinical trials came to a complete halt. At the time, the research division had 12 active clinical trials, two bench-based projects, and a large number of other research projects in progress. Numerous research personnel were then partially or fully furloughed.

Despite all, the research staff focused on ways to continue the essential work of clinical research. Instead of meeting with patients eligible for studies in person, telemedicine technologies, including Zoom, GoToMeeting, and Webex, were used to improve efficiency and safety while maintaining high monitoring standards. Additionally, where in-person visits were required, research staff was provided with appropriate personal protective equipment and clear instruction to minimalize exposure and possible risk of transmission. Although most of the studies are still ongoing, we believe that the measures put in place were well-received by both patients and researchers. Further evaluation should look at differences (if any) in dropout rates and short-term and long-term monitoring.

The use of remote monitoring is vital for the continuation of non-COVID-19 clinical trials. Understanding the detrimental downstream sequelae of these delays, the FDA encouraged flexible ways of restarting trial monitoring efforts through remote visits. For some trial sponsors, setting up the remote monitoring infrastructure was possible despite an interruption in the study period. These adjustments have not been financially feasible for others, unfortunately resulting in the clinical trials' termination altogether.

COVID-19 changed the shape of academic surgery as nothing before. As a sizeable academic institution and leader in orthopaedic research, the research and academic work disruption can profoundly affect many people's lives and careers. First and foremost, our patients had to endure for months musculoskeletal pain quarantined at home. Secondly, the career of the research staff, students, and fellows were affected in quality and quantity, and last but not least, every day of delay in our research can potentially halt the future health of many. However, despite any prediction, there is no exact way to measure what the future impact will be on patients.

These unprecedented events made clear that the common approach to clinical research should and can be improved. New ways were needed, and international efforts were made to 'adapt' to the COVID-19 pandemic by altering the process of clinical and translational research at our institution. As a result, adaptive, pragmatic designs were used to accelerate the process of investigating treatments for COVID-19. Large trials such as the NIAID-sponsored Adaptive COVID-19 Treatment Trial (NCT04280705) and the WHO-sponsored SOLIDARITY trial (ISRCTN83971151) are leveraging adaptive clinical trial designs, in which multiple, prespecified, investigational therapies can be compared with placebo to identify subgroups of patients who respond best to them. Pragmatic trial designs have also been proposed to evaluate therapies on a broader array of patients with the disease and increase the success of clinical trials.

Platform and adaptive trials have been known to trialists and researchers for years, but only recently are making the first few steps in the clinical research world. The reason mainly lies in regulatory pathways and funding agencies' unresponsiveness to adapt to Bayesian statistics. Thus, researchers and industry were hesitant to leave the safe harbour of frequentivistic statistics and 'traditional' trial design. Evidence is clear, and similar trials are arguably the future of clinical trials and research. And if before COVID-19, only a few examples existed in the musculoskeletal world, such as the Arthritis Therapy Acceleration Programme (A-TAP) in the United Kingdom, we expect this to change very soon.

Going forward, we must cement the lessons learned from the pandemic to create meaningful research with an improved design that can jumpstart the future of disruptive clinical research. While the many, mostly unknown, COVID-19 negative impacts on research and human life cannot be overturned, time of crisis boost innovation. We are confident that research, like every other field of knowledge, will be affected by renewed and stronger science.

Another Good Idea Dies In The Nest

Michael Korenfeld

The virus that is responsible for the current COVID-19 pandemic is new, or novel. As such, its behavior in nature and within the people who are unlucky enough to host it is not fully understood. What is clear is that the virus can be recovered intact and viable from the tears of infected people. The concentration of the virus within the tears likely varies between people and likely also varies depending on what stage of the infection people are in. It is also clear that a large percentage of people who are actively infected and also contagious are unaware of their clinical status. It is believed that something like 40% of COVID-19 virus transmission is generated from asymptomatic people.

I work in a private practice around 30 miles southeast of St. Louis. My practice is called Comprehensive Eye Care. We deliver comprehensive eye services to people of all ages. Because we serve a diverse population, these patients have a considerable variety of needs. In the clinic, there have been numerous modifications implemented to help the eye doctors and their staff render appropriate care for this diverse population while minimizing their likelihood of contracting this potentially lethal disease from patients. These precautions are also designed to likewise protect the patients from the doctor and their staff while they are being cared for. The traditional method of sterilizing the tip of the device that touches the eye during the eye pressure measurement is to wipe it with an isopropyl alcohol pad before and after use. This may or may not be sufficient to prevent the transmission of COVID-19 from person to person through the tears, and handling the alcohol pad with an ungloved hand may also be an imperfect strategy. Most practitioners do not use gloves in the eye clinic when checking patients' intraocular pressures. Even if a patient contracted a COVID infection from having their eye pressure checked, there would literally be no way to track and confirm this. Here is an opportunity to create and deploy a "best-practice" solution.

The best strategy is to use a disposable cover that can be affixed to the front surface of the tonometer tip with a forceps, and then removed with the same forceps after the eye pressure is obtained. The forceps would never touch the portion of the membrane that makes contact with the patient's tear film. The disposable cover would need to prevent the virus from traversing the membrane while it is in place and being used. It also would need to have physical and handling properties that protect the practitioner while it is being used.

I have invented and prototyped just such a forceps, and I have tested several commercially available clear membranes that can be reversibly affixed to the front of the Goldmann Applanation Tonometer tip and permit an accurate and precise measurement of the intraocular pressure, when compared to measuring the intraocular pressure with the same device, on the same patient, at the same time of day, without the membrane. The handling of the membrane never puts the practitioner at risk for contamination, and it is easy to handle. The membrane is waterproof, and as such, it is highly unlikely that any virus would be able to traverse the membrane over the 5 seconds of contact that the membrane makes with the patient's tear film. Of course, that would need to be confirmed, but from the armchair, it is very likely a safe and effective prophylactic.

Now I have it, and nobody else does. What happens next?

Valuable, practical, and effective devices "suffer" from the requirement of receiving FDA approval before they can be put into general practice and sold or distributed to the general population. *Proving a treatment that is both safe and effective is, of course, important,* but it comes with an entire portfolio of functional impediments. This is true even when the reason for using such a device is important and immediate, like it is for solutions to the COVID virus challenge. Getting a device FDA approved is both time consuming and expensive. First, a company would be charged with the requirement to evaluate the cost and time for Intellectual Property protection, crafting and implementing a suitable program to achieve FDA approval, future marketing and sales costs, and lost opportunity costs for other products they might develop in the same time frame. Balance all of that against what the product would be projected to generate in future lifetime revenue. If the potential for profitability appears to outweigh these other hurdles, then the entity *might* commence this risky journey. Remember, just because it looks like a product has real promise, there are many opportunities for failure, despite best intentions.

For approval of *this* device, there is not a meaningful ethical dilemma for the Investigator or the IRB; subjects would have their intraocular pressure tested with and without the membrane in place, so there are no placebo treatment risks. Subjects who would enter a clinical trial to validate this device would also not depend on this device to treat existing disease.

Sounds straightforward, doesn't it?

A clear and present need exists. A promising solution is queued up for the final push to implementation. I don't have the funding to bring this to market, do you? I only have a promising solution and the will to try and make things better.

Once again, another likely safe and effective solution will never see the light of day. Can you imagine how many wonderfully useful ideas die in the nest like this?

Welcome to America

Commentary

Research During the Pandemic: Views from Both Sides of the Fence

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Abstract. The SARS-CoV-2 pandemic has affected practically every aspect of life across the globe for the past year or more; the practice of clinical research not the least. Clinician scientists attempting to start or continue work both related and unrelated to the disease itself have faced ethical, oversight, or regulatory challenges. No aspect of the clinical trial enterprise was unaffected. These narratives detail some of the barriers encountered and how the investigators coped (or didn't cope). Common themes emerged, ranging from a need to contribute, which drove the researchers to frustration with real and perceived obstructions (both old and new). The narratives disclose common ethical issues related to research during a pandemic: issues both qualitatively and quantitatively different from other human subject research; challenges both new and novel, as well as those previously seen, but writ large in the face of the crisis. The narratives also offer words of advice from the trenches and speak to successes, both large and small, and to the value of teamwork and focus on a common goal.

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Keywords. Clinical Research, SARS-CoV-2, COVID-19, Ethics, Narratives, Human Subject Research, Placebo, Compassionate Use, Regulatory Burden, Pandemics, Research Personnel

Introduction

"Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China in November 2019, and its designation by the World Health Organization (WHO) as a Public Health Emergency of International Concern on 30 January 2020, the coronavirus disease 2019 (COVID-19) pandemic has significantly affected the economic and social fabric of virtually every country" (Singh, Bandewar, & Bukusi, 2020).

Oddly, the most difficult part of writing this commentary has been devising an introductory paragraph that sums up the dramatic effect of the COVID-19 pandemic on clinical research, much less on the "economic and social fabric" of the world. The COVID-19 pandemic has "created massive disruptions to clinical trial research across the world.

As in other aspects of life, the virus has severely affected the ability to conduct trials in safe and effective ways" (van Dorn, 2020).

These narratives describe the challenges faced by researchers during the COVID-19 pandemic when conducting both COVID-related or unrelated human subject research. Authors were asked to describe any ethical, oversight, or regulatory challenges that they experienced during the pandemic, how they addressed the challenges, and offer recommendations to IRBs, other oversight bodies, or other researchers when reviewing research during a pandemic.

I was asked to provide this commentary because I sit in a rather odd position. I was trained as a pediatric oncologist and clinical researcher. Midway through my career, I made a hard left turn and ended up first an IRB member, then chair, then director. Though I function within the IRB and research ethics world entirely now, I retain my experience with (and therefore perhaps some insight into) the challenges associated with conducting clinical trials in a population with a life-threatening disease.

Further, my institution has always been at the forefront of health security and response to bioemergencies. With the largest biocontainment unit in the country and the sole federal quarantine unit, we took care of Americans with Ebola virus disease (EVD) evacuated from western Africa during the 2014 epidemic and worked with quarantined US citizens airlifted from China during the start of the coronavirus pandemic. During these twin infectious disease events, our investigators led a variety of national and local human subject research projects, which were reviewed by our IRB.

In these stories, I can see the motivations, frustrations, and in some cases, ethical challenges faced by these investigators, both from the point of view of a researcher and an IRB director.

Had to Do Something . . .

A theme in many of these vignettes is the author's (and the researcher's) desire to "do something" in the face of an unprecedented health crisis. Paul Monach says, "I knew I would be low on the list of people to be called in for 'risky' inpatient work . . . but I had to do something; . . . I had to enlist." As Rebecca Wells noted, "The question kept nagging inside my head, 'How can I best help others?' When the pandemic began, I was overwhelmed with a deep desire to serve . . . I felt an urgent need to provide this help as rapidly as possible."

They were certainly not alone. Scientists and medical personnel across the globe who were not directly involved in the care of patients have volunteered time, supplies, and expertise. As research labs and research protocols were halted, the health care workers and scientists who ran and staffed those labs and conducted that research sought ways to help, and online databases of volunteers with technical skills and equipment (like crowdfightCOVID19.o g and covid19sci.org) have arisen.

The desire to serve, so clearly shown in the setting of COVID, is not new, nor should it be surprising. We in the IRB world are often leery of the investigators who use people as a means to an end (laudable as it may be). This protectionist view, and the regulatory system under which we operate, arose as a direct consequence of abuses of human beings: in the concentration camps of the Second World War, in the halls of Willowbrook State School and Brooklyn's Jewish Chronic Disease Hospital, and in the fields of Macon County, Alabama. The regulations that arose sought to "protect human subjects" from unethical research and unethical researchers. But we must remember that the vast majority of investigators want to conduct ethical research that produces good quality information to help others. They want to serve, as do the researchers that composed these narratives. COVID-19 has made that more apparent and desperate.

In these vignettes, the "something" the writers chose to do was research. Some researchers sought to develop therapies to treat the virus, or to ameliorate the clinical syndrome affecting multiple organs. Some attempted to treat the psychological effects and stress related to the pandemic, or a consequence of caring for those with the disease. Some sought to better understand the long-term sociologic effects of COVID-19. In some cases, the research was directly related to studies the writers had been performing prior to the pandemic, or represented only a change in subject population; other researchers completely changed their focus, and used the tools they had available in new and novel ways.

And the act of carrying on, of participating, and helping, also helped scientists cope with the fear and trauma of the pandemic. As Todd Seto notes, "Many of us found value in 'carrying on' in the midst of uncertainty and unease. We found that our clinical trials had a galvanizing effect—they built a common cause for our providers to rally around; they provided a sense of order and purpose; they reaffirmed our identity as scientists contributing knowledge to the larger community."

Though these are mostly stories of success—little successes in terms of being able to continue day to day, or big successes that altered the course of a patient's disease or provided a better understanding of the pandemic or its consequences—those victories were not always easily won.

Non-COVID Research Came "Second" (or Not at All)

The effect of COVID-19 on clinical research has been enormous, with thousands of trials—around 80% of non-COVID-19 trials—being stopped or interrupted (van Dorn 2020). Stay-at-home orders, institutional and sponsor (including NIH) policies, supply shortages, disruption of support services, and altered priorities have all contributed to dramatic slowing or halting of research activities not directly related to the pandemic. Though the need for these halts is entirely understandable, the frustration this engendered is amply displayed in the vignettes

David Altschul notes, "research outside of COVID-19 did take a back seat . . . The clinical research arena suffered, as did the clinical arena in that many patients with diseases not related to COVID-19 suffered as a consequence of this pandemic."

Even research that might have impacted the consequences of the pandemic (such as that related to mental health and stress) became much more difficult to conduct. Studying the delivery of mental health services, Patrick Romani notes, "At a time when mental health research was perhaps most important, universities placed significant restrictions on research practices."

The long-term effects of research halts on the subjects directly involved in these projects, or on the patients who might have bene ted from results of the trials, is not yet clear. Gary Schiller, a medical oncologist, laments "the closure of studies for some of our most vulnerable patients." He notes, "diseases don't disappear by virtue of a pandemic. Even during a crisis, cancer does not take a break".

Barriers to Research

The vignettes present a litany of barriers to conducting any research, even that related to COVID; some have already been noted above. In some cases, the challenges were related to the necessity to avoid contagion and protect subjects, staff, and researchers themselves.

Personnel issues / working from home

Challenges included attempting to conduct trials with diminished staff numbers, or staff working from off-premises. Schiller notes, "not having the regulatory staff on-site proved very difficult. Although they worked from home, many things were not done in a timely manner, documents were not signed, and amazingly, there were no easy electronic options." More generally, and reflecting the theme of the importance of continuing even non-COVID related research, he notes with regret "safer-at-home orders . . . did not define research personnel on clinical trials as essential workers."

The need for the researchers themselves to work from home was seen by most as a barrier. Laleh Coté notes, "Being mostly confined to the home isn't conducive to writing or inspiration, and so it takes me a lot longer to produce something (anything!) than it normally would." But Romani saw a positive side: "My co-investigators and I could meet, develop the surveys, and execute the project at home, at night, or on weekends, whichever was most convenient."

Recruitment challenges

Many authors expressed frustration with barriers to recruiting subjects to trials. Some of these concerns arose from perceived regulatory and "bureaucratic" barriers; we will discuss them later. Others, however, found apathy, or fatigue, or competing interests to blame. Coté, for example, noted, "While recruiting, many people were supportive of these

studies, but explained that there were already plans to survey their own community about their experiences. Others explained that they had too much else to deal with, or simply did not respond."

In contrast, Eric Lenze, conducting a randomized clinical trial of fluvoxamine to reduce immune-mediated complications of COVID, states, "We were also unable to get help from area organizations, who could have told patients about COVID-19 clinical trials but refused to do so. We were surprised by this because we thought there would be a community 'esprit de corps,' and everyone would be interested in finding treatments that would diminish its adverse effects would help everyone . . . In some cases, my research team and I encountered hostility towards clinical trials . . ." Although Lenze offers speculations as to the reasons for this antipathy, I wonder if some part might be related to hesitancy about the "risk" of being assigned to a placebo arm of a clinical trial (as will be discussed below).

Informed Consent

Informed consent is central to the ethical and regulatory framework of human subject research, including clinical trials. Informed consent, in its traditional (and perhaps most effective) form, involves face-to-face contact and conversation between the prospective subject and the investigator. The COVID pandemic has cut right to the heart of this interaction, by interfering with, and indeed, prohibiting, that direct contact, and by requiring the development of new paradigms for the conversation. Altschul notes, "the idea of in-person informed consent became a serious challenge as hospitals restricted visitors for a portion of the time."

Interestingly, some researchers described the need for these novel mechanisms to obtain informed consent as a challenge (most often resolved through cooperation with the IRB and out-of-the-box thinking); however, the complementary need for documentation was often reduced to a "bureaucratic burden" before being resolved as well.

Barbara Yawn notes, "For many sites, the use of e-consent was a barrier requiring new formats, new tools, and in some cases, extensive work with local IRBs . . . We had to redo our consent forms not just to accommodate the e-consent format but to include information on protecting participants from study-related spread of COVID and to accommodate mixed virtual and in-person visits."

Regulatory Burden / Bureaucratic burdens

Not surprisingly, some authors cited regulatory (or stated less kindly, "bureaucratic") burden. Westyn Branch-Elliman and Paul Monach note, "we were forced to develop more complicated and cumbersome processes, all in the name of collecting proof of a wet signature on a page from the patient or legally authorized representative." Monach bemoans, "cumbersome and changing recommendations, put in place by people who never have to interact with a patient or treating physician, has made the conduct of our trial nearly impossible. Everyone who could in uence the trial from a distance slowed it down."

Seto notes that "the bureaucracy of research regulation and compliance, built over decades to minimize institutional risk and maximize human subjects protection, was poorly suited to match the rapidly evolving clinical milieu of the early pandemic."

What was surprising though, was the infrequency of the complaint. When I was asked to read a series of narratives by researchers describing the ethical, oversight, or regulatory challenges they faced during the COVD-19 pandemic, I anticipated a certain amount of fault attributed to the overly bureaucratic, obstructionist tendencies of regulators and IRBs in particular. Such complaints are often well-grounded, but nonetheless sting. I was grateful to nd remarkably little in these stories.

There is certainly truth in the observation that regulations and regulators slow the pace of research. There is also truth in the assertion that some of these barriers are unnecessary. However, there is, in some of these narratives, a sense that research is good, and therefore, anything that stands in its way (including protections for subjects) must be bad.

Also apparent in a few of these narratives is a related ethical trap; that is, the expectation that whatever intervention is being proposed in the research is better than nothing. This is the classic formulation of therapeutic misconception; that is, some authors seem to "deny the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself" (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987). It is perhaps forgivable among medical practitioners desperate to offer something to their patients, but this must always be guarded against by scientists.

Teamwork

As a counterpoint to concerns about bureaucratic barriers and burdens, many narratives spoke of the ultimate triumph of teamwork between researchers and the IRB and human research protection programs.

Various authors spoke of "the efficiency of our university's COVID-19 committee . . . and our Institutional Review Board (IRB) which accelerated their review process" and "*ad hoc* meetings to help expedite our study reviews." Rebecca Wells notes, "the IRB office was open, operational, and studies related to COVID-19 were receiving top priority . . . Efficient responses and anticipation made me feel like we were working on the same team, side-by-side, all of us together."

In the face of a bioemergency, the need for rapid, responsive and quality ethics and regulatory review is well recognized (Saxena et al., 2019). During the Ebola virus epidemic in 2014, our IRB utilized a rapid review model to review and ultimately approve the use of investigational drugs for critically ill patients with the disease. During COVID, we utilized the same paradigm, now as the single IRB for the Special Pathogens Research Network of the National Emerging Special Pathogens Training and Education Center (NETEC). That other IRBs and HRPPs were able to function in this manner is gratifying, and speaks to what we have called the "all hands on deck" approach to this sort of crisis (Lowe et al., Submitted).

Central to successful rapid review is preparation and communication. Recognizing this, Romani advises, "I would heavily encourage researchers to connect with their IRBs early and often to ensure understanding of preferred formatting characteristics of applications and to communicate idiosyncrasies of applications to ensure rapid review." I could not agree more.

Ethical Issues

I am not a trained bioethicist (but I have, through osmosis and contact with greater minds, acquired the fundamentals of research ethics). However, all astute observers recognize that research during a pandemic poses ethical issues both qualitatively and quantitatively different from other human subject research; challenges new and novel, as well as those previously seen, but writ large in the face of the crisis (Nuffield Council on Bioethics, 2020; World Health Organization, 2010). Two of these issues recurred in several of the narratives and are worth mentioning.

Research vs. compassionate use

The use of new or repurposed drugs as "therapy" in the setting of a life-threatening illness has been a feature of the coronavirus pandemic, a result of the lack of effective therapies in the face of a mounting global death toll (and exacerbated by the flurry of uninformed tweets and weaponized misinformation).

The ethical argument in favor of off-label (and off-clinical trial) use of drugs is similar to that offered for "right to try" laws and programs: patients (and in their fiduciary role, physicians) should have a right to mitigate extreme suffering and to enhance self-preservation. "As rational actors, patients . . . should be entitled to utilize their own risk-benefit thresholds in deciding whether to consume such products" (Darrow, Sarpatwari, Avorn, & Kesselheim, 2015).

However, using these drugs outside the context of a randomized clinical trial impacts the ability to learn about both benefits and risks associated with

these therapies and use them more effectively and more safely (Kalil, 2020). The failure to generate useful information about therapeutic interventions during the EBOV epidemic in 2014 highlights the risk here.

Branch-Elliman and Monach observe in their trial of IL-6R inhibition as an adjunct treatment for COVID, "The question was whether to use medications off-label based on limited anecdotes or to conduct a clinical trial . . . There was a desire by many, both among research leaders and some clinicians, for a "clinical trial" banner, so that patients would be appropriately informed about the potential for a lack of benefit—and potential for harm—associated with almost any COVID-19 intervention."

Seto noted in his trial of hydroxychloroquine and tocilizumab "For some of us, clinical equipoise—when there is professional disagreement among the community of expert practitioners as to the preferred treatment—was suf cient to justify enrolling patients into randomized clinical trials. For others, it was not."

Ethical study design / use of placebo

Similar angst arises when considering the justi - cation for a placebo (or more accurately, a "best supportive care") arm.

In the narratives, Lenze chose to use a placebo-control design since it would result in "providing more high-quality evidence than can be obtained from observational studies"; and Branch-Elliman and Monach because it would result in "bolstering scientific validity for subjective outcomes.

However, the latter authors note, "we witnessed psychological distress not only among patients and their relatives, but also among treating physicians as evident in immediate abandonment of the scientific principles that they had supported during design of the trial. When patients were randomized to standard care, physicians quickly revolted, and requested open-label use of the unproven study drug".

The ethics of using a placebo arm (or again, more accurately, about using a "best supportive care" arm) in a randomized clinical trial has been debated for decades; and similar arguments arose during and after the 2014 EVD epidemic (Adebamowo et al., 2014). The ambivalence expressed may represent the fundamental contradiction between the dual roles of physician and scientist, and as noted above, may lead to hesitancy to enroll patients in randomized clinical trials (or even to discuss those trials).

Conclusions

Describing the effect the coronavirus pandemic has had on the fabric of society remains, for me at least, an exercise in futility: it defies mundane language. In these narratives, though, we see glimpses into the human drama around a narrow slice of the activities of my life, and the lives of other practitioner-scientists. And so, perhaps, we can see a shadow of the bigger picture.

These narratives are in some ways strikingly similar to each other, and in other manners, very different. We see this defining moment of a generation through different lenses, and we take away different lessons. Within the very narrow scope of this series, the effect of the pandemic on researchers, I believe I see cooperation, teamwork, and a joint understanding of the importance of both the subject of the research and the research itself.

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Commentary

Human Research During the COVID-19 Pandemic: Insights From Behind-the-Scenes

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Abstract. The researchers' stories collected here demonstrate how many ethical and practical challenges routinely associated with conducting human research were amplified during the COVID-19 pandemic. These challenges include designing studies to minimize risks and maximize potential benefits, working with institutional review boards (IRBs), recruiting and enrolling participants, obtaining valid informed consent, promoting data integrity, managing budget constraints, and finding time to fulfill research obligations along with other duties. By offering insights about not only the barriers and challenges researchers encountered but also the creative solutions they and their colleagues found to conduct research, this behind-the-scenes peek at researchers' experiences helps us to identify barriers and potential lasting improvements for human subjects research even in the best of times.

Funding. The work to put together this symposium was supported by the National Institutes of Health [3R01AG058254-03S1 (James DuBois, principal investigator)].

Keywords. COVID-19, Informed Consent, Institutional Review Board, Research Subjects, Research Ethics, Human Subjects Protections, Research Personnel, Pandemics, Ethics Committees, Narratives

The COVID-19 pandemic made perennial ethical issues throughout society "louder." The researchers' stories collected here demonstrate how many ethical and practical challenges routinely associated with conducting human research were amplified. These challenges include designing studies to minimize risks and maximize potential benefits, working with institutional review boards (IRBs), recruiting and enrolling participants, obtaining valid informed consent, promoting data integrity, managing budget constraints, and finding time to fulfill research obligations along with other duties. These personal narratives are from individuals engaged in research involving everyone from children to older adults and from generally healthy to seriously ill individuals. Their studies concerned mental health, physical health, and the social impact of the pandemic. Yet, there are many similarities between the challenges they faced and the solutions they found. The stories also reveal some significant differences. While some of the stories illustrate what it was like to be met with overall support for research and a collaborative spirit, others report hostility toward research, overwhelming barriers to collaboration, or simply a lack of interest in or appreciation for research. This

behind-the-scenes peek at researchers' experiences helps us to identify barriers and potential lasting improvements for human subjects research even in the best of times.

Running: The Race Is On

Whether they were designing new studies or nding ways to continue existing research in the face of new and ever-changing circumstances, the authors describe a frenetic pace and a deep desire to "do something". As Westyn Branch-Elliman & Paul A. Monach note, "Under normal circumstances, the process of designing, re ning, and conducting a clinical trial would take months, at least. However, with COVID breathing down our necks, time was short. . . . With members of the team working literally around the clock . . . we were able to advance from a 2-page summary 'pitch' to IRB approval in 6 days and enrollment of the rst patient 4 days later." Similarly, Eric Lenze's team "recruited [their] rst participant only 16 days after [their] rst conversation about using uvoxamine for COVID-19."

Common ethical, practical, and scientific questions took on new dimensions and significance in this environment, and they had to be addressed quickly. Many stories addressed the importance of identifying, minimizing, and justifying research risks, including risks to third parties. Research typically involves uncertainty regarding risks, and there is significant disagreement about the level of risk that is permissible in research, which risks should be treated as "research risks," and how to calculate research risks, especially in the face of uncertainty (Binik & Weijer, 2014; Kopelman, 2004; Press & Rogers, 2017; Rid & Wendler, 2011). The level and scope of uncertainty the pandemic posed was extraordinary. Several authors faced concerns about whether research was justifiable given the dire circumstances. Even though "[c]linicians widely acknowledged that no available drug had sufficient evidence to support indiscriminate use in a purely clinical setting," Branch-Elliman and Monach report that many thought it best to use "medications off-label based on limited anecdotes" rather than to "conduct a clinical trial." Similarly, Rebecca Hendrickson recounts efforts to study acute stress disorder (ASD) among healthcare workers, a condition for which relatively little research has been done. She was asked whether it was permissible to withhold an unproven intervention from anyone in the study. The IRB reviewing her research also asked whether studying healthcare workers in distress "posed a risk to the health care system overall." Ironically, no one seemed concerned about the risks to the system of having a healthcare workforce experiencing ASD; they were concerned only about the risks associated with trying to study and mitigate the problem.

Research risk assessment typically involves risks to participants and, to a lesser extent for most research, risks to third parties. Risks to researchers themselves are rarer still, yet the early days of the pandemic changed that. As Lauren Southerland, Jennifer Frey, and Russell Williams note, "We had so little knowledge of how this virus worked in the first few months. Who needed to be protected? The staff member with the newborn baby or the one with comorbidities?" Designing studies required researchers to consider and mitigate unusual risks: "We took signed paper consents, bagged them in gallon-sized plastic zipper bags, wiped them down with disinfectants and then let them sit for 2 weeks in the hope that any virus would be dead by then" (Southerland, Frey, and Williams).

In addition to deciding *who* was at risk and how best to minimize risks, researchers and IRBs had to determine *how* to balance risks with other interests, such as promoting data integrity, which is important for knowledge generation. Barbara Yawn describes a plan to collect data remotely to decrease the risk of transmission. The plan was "acceptable to several primary care practices and research oversight groups," Yawn explains. "[B] ut not to "our academic pulmonology investigators and the experts on our DSMB [who felt] that at home pre- and post-bronchodilator spirometry could [not] be done with sufficient accuracy to meet the needs of our study."

The task of identifying, minimizing, and balancing risks and potential benefits took on new

and unusual dimensions during the pandemic in research as in virtually every aspect of life.

Running on Empty

For many people, the pandemic led to a prolonged period of running on empty. In varying ways and degrees, we lacked (1) energy and time, (2) material resources, and (3) information in which we could be confident. The researchers who shared their stories were no exception.

The pressure and commitment to keep research going while short-staffed, and in many cases with added responsibilities at home, is palpable. The resulting stress was compounded by additional challenges that would show up without warning. As Laleh Coté poignantly commented, "I can't choose when my family has a rough week, when news will arrive of another person who has died, . . ."

The shortage of PPE and medications created significant challenges for many researchers. For Branch-Elliman and Monach, "securing a medication amidst supply chain barriers . . . necessitated completely revising the study within the 6-day period of design." Unexpected expenses placed additional burdens on researchers since, as Southerland, Frey and Williams note, "Research budgets didn't account for the extra costs of cleaning supplies and PPE." Some researchers, such as Todd Seto, who were studying drugs that were being used off-label in their institutions, found that by enrolling patients in a trial to study outcomes, their institution "had to pay for the cost of the study drugs." This made it seem they "were being 'punished' for doing the right thing—offering these medications as part of a randomized controlled trial rather than usual care." Off-label use would have been reimbursed.

Clinicians and patients often make decisions in the face of limited information and uncertainty (see, for example, Martinez 2012.) This is particularly true for individuals with conditions that have not been thoroughly studied, when people are part of groups that were not well-represented in research, and for members of populations routinely excluded from research, such as children and pregnant women. COVID-19 made this true for everyone. The stories here reveal two different approaches to uncertainty and the information deficit everyone faced. The authors' commitment to using established research methods to reduce uncertainty and improve long-term outcomes stands in sharp contrast to what some of them encountered—unstudied interventions adopted quickly and described as new standards of care.

The authors tell not only of the need to study treatments for COVID-19 but also other conditions that emerged during the pandemic, such as the ASD Hendrickson observed among healthcare workers, and the hastily adopted adaptions to healthcare delivery whose efficacy was unknown. Patrick Romani describes the importance of evaluating partial hospitalization programs (PHP) that were quickly shifted to telehealth, something that, to the best of his knowledge, had not been done before.

The information deficit under which everyone was operating, particularly in the early days of the pandemic, had special implications for research. It motivated the need for research, but it also created pressures to just "do something" and provide everyone with anything that might help. This resulted in some hostility to research, as described below.

Running With the Wind at Your Back Versus Running Against the Wind

The authors describe moving as expeditiously and thoughtfully as possible to continue existing research under new circumstances or to get new research designed, approved, and underway. Their stories highlight the difference between those whose efforts were supported, such that they were running with the wind at their backs, and the experiences of researchers forced to run against the wind.

Several authors describe positive experiences with their IRBs, who adapted quickly and worked hard to foster ethical and compliant research in the face of adversity (see, for example, Altschul, Lenze, Branch-Elliman and Monach). Seto's IRB, for example, "held ad hoc meetings to help expedite . . . reviews . . . and it took 7 days to go from conceptualizing [their] hydroxychloroquine study

to enrolling [their] first patient." Rebecca Wells describes a particularly helpful response. She says: "I reached out directly to our IRB director, a reliable and resourceful leader . . . [and] received an immediate response that the IRB office was open, operational, and studies related to COVID-19 were receiving top priority. I received swift responses to all my questions, with specific recommendations and concrete advice." She describes ongoing prompt support through the online submission process and as additional challenges arose. Even though "no one was working in their hospital offices . . . IRB officers communicated rapidly via email and provided home office numbers for availability." Wells describes feeling as though "we were working on the same team, side-by-side, all of us together versus the sideline clock ticking." Clinicians caring for patients also were instrumental in facilitating some research. Branch-Elliman and Monach acknowledged gratefully the role "clinical colleagues, who were working in the COVID units [who brought] consent forms to the patients' bedsides during morning rounds, so that we could avoid redundant exposures and use of PPE."

Other authors encountered apathetic "not my job" attitudes (Lenze) and outright hostility toward research on the part of clinical colleagues and other healthcare or community organizations. The desire to "do something" led many clinicians to provide various interventions off-label and with little-to-no evidence of efficac . They were unwilling to consider enrolling patients in research. Even clinicians who had participated in designing the studies and agreed to participate "quickly revolted" "[w]hen patients were randomized to standard care,. . . . and requested open-label use of the unproven study drug within 24 hours—even in stable patients"(Branch-Elliman and Monach). Seto describes similar challenges in studying hydroxychloroquine, where "disagreement on the role of physician autonomy vis-à-vis the broader professional community, the meaning of 'evidence-based,' the obligations of physicians to their patients, and the ethics of randomized controlled trials during pandemics," replaced rigorous discussion of the merits of this unproven intervention. Seto's example illustrates much of what is at stake in debates over the role of equipoise in the research ethics literature (Freedman, 1987; Gelfand, 2013; Gifford, 2000; Gifford, 2007; F. G. Miller & Brody, 2007; F. G. Miller & Veatch, 2007; P. B. Miller & Weijer, 2007; Veatch, 2007)

Lenze sought help from community partners to share information about outpatient research on COVID-19, but they "refused to do so." He was surprised since it seemed that "the organizations would be interested in finding treatments that would diminish the virus's adverse effects and help everyone." Moreover, we were not asking for organizations to make much of an effort, such as recruiting and consenting (this is the most time-consuming and difficult task in clinical trials). . . . [T]hey were unwilling to participate even in terms of allowing us to post advertisements or to include a study flyer in their paperwork given to patients." The county health department went so far as to say that "it would be unethical for them to even tell patients about the existence of COVID clinical trials."

As Coté found, some people who could have helped her recruit survey participants "explained that they had too much else to deal with . . ." and could not take on one more task. This is a feeling with which many if not all readers likely can identify.

Left Out of the Race

The stories here tell of a widespread race aimed at reducing uncertainty, improving outcomes, and serving the interests and needs of many people in the face of the pandemic. They also reveal examples of groups that were left out of the race, or whose interests were trampled on or dismissed in the stampede. These include (1) people with conditions unrelated to COVID-19, (2) healthcare workers facing mental health struggles in the pandemic, and (3) groups who were intentionally or unintentionally excluded from or greatly under-represented in research.

There seemed to be two categories of patients during the pandemic, especially during the first

six months or so when access to healthcare was severely curtailed in the face of uncertainty about transmission and PPE and other shortages: people with COVID-19 and everyone else. The latter group's needs largely were relegated to the "maybe later" pile. Several authors remind us that many patients' healthcare needs went unmet and were largely disregarded because "elective surgeries were canceled. . . ." (Altschul) and much outpatient care was postponed for months or skipped altogether. In addition, clinical research on everything but COIVD-19 was halted or significantly restricted. Yawn saw "all primary care research . . . suspended. . . . until late in the first quarter of 2021 due to the need for all attention to be focused on COVID-related care." Reflecting on "the closure of studies for some of our most vulnerable patients," Gary Schiller argues that "[c]losing studies due to regulatory challenges was. . . . wrong. . . . [because] diseases don't disappear by virtue of a pandemic. Even during a crisis, cancer does not take a break. . . ." and " . . . our patients do not have the luxury of scheduling their diseases outside a pandemic epoch . . ."

The barriers Hendrickson faced in attempting to conduct research that was related to the pandemic but not to a COVID-19 diagnosis raises concerns about whose needs were deemed worthy of a response and whose were not. Her story also suggests that sometimes contradictory understandings of research risks undermined the interests of certain populations. The ASD among healthcare workers Hendrickson observed was related to the pandemic but not part of the COVID-19 diagnostic "bucket." She notes that ASD is difficult to study, and often it is treated the same way PTSD is treated, including prescribing prazosin. Hendrickson proposed a study that "would be generating the first structured clinical trial data to address the efficacy of this intervention for, in particular, the acute sleep-related symptoms of acute stress disorder." The study would be the "first direct test of whether treatment with bedtime prazosin during or immediately after a traumatic stressor could decrease the risk of PTSD at 6 months." The IRB's negative and contradictory concerns left her confused. Much as with clinical researchers who wanted to bypass research on COIVD-19 patients and just try something, Hendrickson was "asked whether we could really justify having a placebo group if the need were as great as we indicated." Yet, "moments later, [we were also asked] how we could justify using an 'experimental treatment' where there wasn't yet clear data to support its use in this specific context." Research on patients with COVID-19 with far less evidence to support it was being approved routinely.

Ultimately, Hendrickson describes the hostility toward her work as reflecting disregard for the interests of healthcare workers: "a theme throughout these decisions was that health care workers working during the pandemic were no longer being viewed as people, for whom the traumas they were experiencing could exert a real, personal toll, but instead as workers, whose human responses to trauma could be ignored." The IRB even asked whether they "[c]ould . . . require permission from participants' employers before they were allowed to enroll."

Recruiting and enrolling representative participant samples is an ongoing problem for researchers even under ideal circumstances (Bernard, Clayton, & Lauer, 2018; Ford et al., 2008; Hwang, Randolph, & Bourgeois, 2020; Kopelman, 2000; MacKay & Saylor, 2020; Mazure & Jones, 2015; Tahhan et al., 2018; Weiss, Koepsell, & Psaty, 2008). This was amplified in the pandemic. Some of the usual groups were excluded from many studies, including older adults—especially those living in long-term care or assisted facilities, children, and pregnant women. In many cases, however, exclusion is not intentional. For some individuals, the virtual research context impeded participation. Likely, those same people faced barriers in accessing routine health care in the telehealth-only world. As Yawn found, the shift to telehealth also meant that some researchers could not continue their work because their clinical environments did not support any form of telehealth or they were forced to shut down altogether due to financial losses

Beth Prusaczyk laments the difficulties faced in trying to include a diverse pool of participants to

study "the pandemic's impact on older adults from a 'whole-person' perspective." Her team "decided to make a concerted effort to recruit older adults who were low-income, Black or African-American, or identified as LGBTQ." Their goal was to ensure representation not "only [of] more privileged older adults who were likely to navigate (and literally survive) the pandemic better than these other groups." Prusacyzk faced numerous, sometimes insurmountable, logistical challenges: "Fully virtual/remote research, whether done out of convenience or necessity, brings with it a significant cost to recruiting and enrolling diverse populations who are often excluded from research to begin with." This limited who could participate and, ultimately, whose experience of the pandemic would be shared.

While we heard of many important advances in treating patients with COVID-19 and successful adaptations of research and clinical care, some of the stories remind us that many needs went unmet and that research participant samples often were not broadly representative.

Conclusion

The stories give us a rare glimpse into life behind-the-scenes in different research environments. Scientific publications often give the false impression that research is a tidy, linear activity. The pandemic introduced countless additional complications for researchers, some of which the authors describe. Even in "regular times," research is more complicated than brief publications suggest.

There is much to learn from the authors who generously shared their experiences of conducting research during the COVID-19 pandemic. First, there is a difference between "how we do things" and "how things must or ought to be done." Often, there is more than one "right" way. For instance, we must distinguish between ethical obligations themselves and the practices typically used to "operationalize" or satisfy those obligations. It is a mistake, for example, to equate the ethical obligation to obtain informed consent with a standard practice that involves pieces of paper hand-delivered to and signed by a potential participant, possibly with an additional witness physically present. Conflatin ethical obligations with practices used to meet those obligations can make it difficult, if not impossible, to adapt to changing circumstances or even to meet the needs of different participants. Similarly, there might be more than one acceptable way to conduct study visits and collect data, even within a single study. Perhaps nding ways to reliably obtain informed consent and collect some data over the phone or using telehealth platforms as an alternative for some participants, while accommodating those for whom in-person study visits are best, will make research less burdensome, allow a broader range of people to participate, decrease missing data, and improve the overall quality of research results.

Second, clinicians, regulators, and society at large should recall that the severe information deficit regarding preventing viral transmission and treating COVID-19 was terrifying and resulted in many problems. Patients and clinicians regularly face varying degrees of information deficits even outside the pandemic. Some conditions have not been studied or have not been studied extensively. Others have been studied but effective treatments have not been found. In yet other cases, standard treatments for those conditions have not been tested in representative samples. For many of the people receiving treatment, there is little or no evidence about the safety and efficacy of those treatments in people like them, resulting in calls to make research more inclusive to improve the generalizability of results. Failures to attend to inclusion in research and to the generalizability of research results leaves many patients and clinicians facing severe information deficits even in the best of times

Third, collaboration, cooperation, and coordination are essential for efficient and effective research. This includes partnering across institutions and even countries to conduct larger rigorous studies, working with regulators and human research protections professionals, and engaging communities to determine how best to protect the interests and rights of participants and obtain the most reliable information to advance knowledge and health. This overall goal also has important implications for transparency and data-sharing.

These typically-untold stories of research can help us better to understand why even in good times, research gets derailed, why recruitment might be slow, why data might be missing, why many important questions go unanswered and so on. They also can reveal how day-to-day, seemingly mundane, decisions, attitudes, and behaviors can promote or undermine human research. Improving the scientific and ethical quality of human research is a choice, and these stories both motivate and inform that choice.

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Commentary
Perseverance

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Abstract. The COVID-19 pandemic disrupted and displaced the old normal, necessitating adaptation. The narratives in this issue of NIB give us a glimpse into the experience of conducting research during a pandemic. The authors were on a mission to pursue research despite the challenges the pandemic imposed. They described difficulties of the Institutional Review Board process and the necessity of asking for accelerated IRB approval. The authors also discussed challenges they faced with research participant recruitment during a pandemic and concerns about keeping staff safe from the risk of transmission. The authors adapted and adjusted to the personal and professional restraints the COVID-19 pandemic placed upon them. Despite these difficulties, the authors remained committed to maintaining the integrity of their research.

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Keywords. SARS-CoV-2, Research Ethics Committees, Pandemics, COVID-19, Research Participants, Human Subjects, Narratives

Introduction

"I remember the last day my life was 'normal,'" writes Westyn Brandt -Ellison and Paul A. Monach in their collection of these real-life reflections into the authors' professional and, at times, personal lives. Our normals were changed, dislocated, buffeted. Will there be a better normal when we emerge from the COVID-19 pandemic?

The COVID-19 pandemic disrupted and continues to displace the old normal. The impact on our authors and their research careers was real, palpable. The impact also necessitated adaptation. The common thread of these stories was a dedication to a mission. A mission to pursue research despite the challenges the pandemic imposed. Adaptation evolves from adversity and our authors adapted. The common, contingent frame around all these writers and their research was the confounding difficulties of the Institutional Review Board process. The common adaptation was how they reacted and adjusted to the restraints the COVID-19 pandemic placed upon them and how the requirements of the IRB process constrained their research mission. Fundamental to them all was their need to adapt within the confines of, at times, a rigid rubric of institutional protocols.

Institutional Review Boards exist by necessity. All our authors recognize this need. IRBs provide a fundamental assurance throughout the research

world. By design, IRB boards do not necessarily adapt to circumstances but rather provide a form of governance agnostic of geo-political or health-related events. The COVID-19 pandemic arrived with no playbook for researchers or Institutional Review Boards to reference. Such an event was certainly not written into a research protocol and was not part of study contingency plans submitted to an IRB for approval. What does one do when faced with such circumstances?

There was an impressive range of background and research focus from our authors. They all faced similar challenges, however, on how to change their research protocols to adjust to the new normal.

Adversity: Values Maintained

Laleh E. Coté reflected at the pace of change as communities, governments, health systems and the pharmaceutical industry reacted to the pandemic. Crisis, however, can create opportunity. New protocols were written and addenda to existing protocols submitted. Others pivoted to new studies that incorporated the COVID-19 pandemic into their research. New questions were raised and particularly those studying environmental stress suddenly found themselves living within a historical event from which to collect new data.

COVID-19 also had its personal impact on the individuals who had to navigate their personal and professional lives amid the uncertainty and seemingly relentless spread of the SARS-CoV-2 virus. The same threat that was encompassing the world was the very same threat that was present in their personal lives. There was nothing existential about this crisis. It was in real-time. The virus being studied was the same virus that was threatening the personal lives and health of the researchers themselves—the very same *risk* that some were studying.

The integrity of the process, however, prevailed. IRBs remained in place and their counsel and perspectives incorporated into research protocols. This was not without frustration. Some IRBs did not seem willing to adapt to the new reality. It would seem a logical matter to convert physical visits to virtual and paper consent forms to electronic; but implementation in some cases was problematic. Barbara Yawn experienced IRB push back when she wanted to conduct virtual visits and consent participants online. She wrote, "For many sites, the use of e-consent was a barrier requiring new formats, new tools, and in some cases, extensive work with local IRBs to approve not only specific e-consent tools but also garner support for the *concept* of e-consent, even for our minimal risk study." HIPPA added further challenges, whether in communications with colleagues at home or installing HIPAA compliant software into work laptops. Much non-research patient care pivoted quickly to telemedicine. Why could some IRBs not recognize the need to adjust protocols to enable remote monitoring? Additionally, institutional bureaucracy invariably slowed progress and efforts to adapt. A common refrain among the stories was challenges with the informed consent process. Appalling research abuse resulted in the Belmont Report and eventually, established rules that protect human research subjects participating in federally funded research projects (Breault, 2006).

Informed consent spawned the IRB establishment that is now the cornerstone of human research. Many authors, however, struggled with their IRB boards and their own study protocols to adapt the informed consent process to the realities of the pandemic. Simple protocols such as a witnessed hand signature required a significant process change and approval. Some researchers chose to maintain a paper process that involved mailing consent cards or documents, while others created an electronic process that then necessitated additional exceptions approval.

Ethics boards were convened to solicit input on amended research protocols. IRB decision making was slowed while awaiting some clarity on treatments, more current COVID-19 epidemiological trends, vaccination data, or treatment options. Clarity, however, rarely arrived with the resolute precision necessary to move forward at the pace the pandemic seemed to require. Like most of us, recognition and understanding of the length of time that COVID-19 would continue to impact our daily professional lives were delayed.

Invariably, a dynamic tension developed between those doing the research and those whose purview is to oversee the qualitative value of the research and whose responsibility is protective oversight of study subjects. While this dynamic is ethically essential, the frustration of not being able to move one's research forward added stress to those on the front lines of research projects. State Departments of Health and others with jurisdiction imposed additional obstacles creating a perception of ethical paternalism. These frustrations were, of course, in addition to the isolated world we all found ourselves as we navigated our and our family's risk of exposure. Particularly in the early phases of the pandemic, there was not the understanding of viral transmission that we now have. This uncertainty about the true risk of viral transmission and communal spread to and within a family, patients, and colleagues added to the researchers' professional angst. Many likely know one or more individuals personally who contracted or succumbed to COVID-19.

A central question: did the IRB process and its requirements add to the adversity? A common, though not universal, refrain would be a respectful yes. All the authors felt an urgency to move their research forward. At the same time, they all valued and respected the IRB. Oftentimes those on the IRB board were colleagues. IRBs are not implacable obstructionist committees rather partners in scientific integrity. Could they have better recognized the unique circumstances of the pandemic and recalibrated their process? What is interesting was the range of experiences between the researchers and their IRB board. Some of this variability was institutional and dependent on local leadership but other was the IRB's willingness to adapt to the circumstances. Personal relationships with IRB members appeared to matter.

From Rebecca Wells: I reached out directly to our IRB director, a reliable and resourceful leader whom I had come to know over the last 8 years at my institution as someone always ready to offer assistance. I wanted to ensure full clarity with these nuanced questions from the onset to ensure a smooth IRB process and rapid approval . . . I received swift responses to all my questions, with specific recommendations and concrete advice.

Eric Lenze offers some constructive considerations on lessons learned and how to improve the process. One would be to create a centralized and standardized IRB process. Such a conversion would reduce unnecessary bureaucracy and standardize an, at times, idiosyncratic process. Another would be to work collectively towards a cultural change to emphasize the importance of public and patient engagement in research. He points out the interesting exception the public has towards oncology research. Beyond that, public interest wanes. Broader public awareness and interest in participating in research trials throughout the medical research community would engender broader recruitment and interest. As a practicing clinician myself who sees patients in the hospital and office daily, I regularly ground my treatment discussion with patients on published research. I rarely go a day without saying to a patient, "the published research supports" one option over another or "the best, scientifically grounded way forward" is this. Such fundamental, factual, and research-based reasoning is essential to patient care throughout a care continuum. Why then is there not more public engagement?

This may be one interesting legacy of the pandemic. The media was prolific with emerging SARS-CoV-2 treatments and the progress of the vaccination efforts (Anwar, Malik, Raees, & Anwar, 2020). In general, the public likely learned more about the phases of FDA drug development than had been known before the pandemic. Additionally, some members of the public served as volunteers in vaccine development. The compressed timeline of vaccine development and deployment notwithstanding, there was intense public and media scrutiny around the vaccine testing with each phase receiving headline news. Adverse reactions of vaccine trial subjects in some ways received disproportionate attention, but more of the public hopefully now understands the scientific rigor that is essentially assumed by the research community. Potentially, the greater awareness of the process of drug development and research protocols will make

for easier conversations to engage the patients and the public in the future.

Commitment to a Cause

Science is iterative. It builds on past discovery and is fueled by curiosity. The pandemic pushed the authors to find solutions to the obstacles and challenges the pandemic posed. They pushed forward against uncertainty and, at times, resistance. Our authors respected the IRB role but at times felt frustrated by the intractability of the IRB to adapt to the fluid reality the pandemic created. Any research that required direct patient contact or incorporated testing or sample collection had to navigate local, state, federal, and institutional protocols. A simple blood draw required additional layers of safety for patients and staff. PPE needed to be purchased. Patient and study subject screening processes needed to be installed. One researcher, Barbara Yawn, had a study involving collecting spirometer data; this high aerosolization situation was a particular risk given the method of spread of COVID-19. Protective creativity prevailed to enable research studies to move forward.

Failure to adapt meant failure to progress their research and lose enrolled patients, lose momentum to recruit patients, and deviate from the IRB protocol jeopardizing the integrity of the research. We may not truly know the impact for 5 to 10 years. For our authors, however, heuristic creativity prevailed. Many institutions created COVID-19 task forces that were empowered to address the very challenges faced not only amongst the researchers but also throughout their institutions. Such a commitment to moving the research process forward must be commended.

Adaptation: Blurred Boundaries

COVID-19 changed our workplace. Boundaries between home and office blurred. These changes were not unique to the scientific community. Our authors, however, well described how their professional lives intermixed with their personal environments. Likely underappreciated in the narratives is the impact maintaining their professional research careers had on their personal lives. In *Nature Human Behavior*, Myers et al. write that "shelter at home is not the same as work from home" (2020). In their survey of research scientists, they found a disproportionate impact of research productivity based on the type of research, gender, and personal circumstances. Logically, the bench sciences were the most impacted while those involving less equipment intensity fared better. Additionally, female responders to the survey reported less time devoted to their research when compared to their male colleagues. Having young dependents seemed to be the single largest variable impacting productivity. The reality of the survey was bourn out in the anecdotal reports of our authors.

When you work in a physical office or laboratory, the act of leaving the environment at the end of the day logically translates into an intellectual disconnect from work. With researchers finding themselves working from home, the frustrations of work and the frustrations of everyday life build upon each other in a different way. It is difficult to focus one's intellect solely on academic work. This is a situation in no way unique to the researchers during the past year. However, the mental health toll of the pandemic is likely underappreciated and comes out as a background refrain in these researcher's experiences.

Lessons Learned

The recent NASA Mars rover landing was an extraordinary accomplishment. The rocket carrying the rover launched July 30, 2020, in the midst of the pandemic though the research, development, design, and testing were years in the making. Pausing the project was not an option (National Aeronautics and Space Administration (NASA), 2020). Such was the case of many of our researchers. Their research was active and underway. The Mars rover name, Perseverance, could be aptly applied to our authors.

Perseverance and creative response to adversity took many forms in our personal lives as well. Zoom went from a relatively marginal activity to

a universally recognized verb. Untold in the news were many of the small heroics. Families helping families and neighbors helping neighbors. Operatic singers threw open the shutters of their balcony windows and serenaded the isolated. Horns and pans clamored at set hours in support of firs responders. Banners fle , chalk art drew, and the warmer side of our beings shined through.

Todd Seto looks forward to incorporating the lessons learned in adapting to the pandemic to develop a process for multiple institutions to come together and develop multi-center clinical trials more easily. In the midst and uncertainty of the pandemic, institutional collaboration understandably slowed and in some cases ground to a halt as each contended with the local and on-site challenges imposed by the pandemic. In response to this, a centralized repository could be created to standardize methodology and protocols and streamline access for research projects large and small.

The "galvanizing" effects these challenges could provide to research teams were one positive consequence. Research teams came together to solve challenges imposed by the pandemic as they worked toward a common goal. The fact that the goal was toward a common good provided validation, as scientists worked toward a larger, greater purpose.

Mental health research merits particular mention in this context. Many of our authors work and conduct research in the mental health field The pandemic posed inherent challenges with patient enrollment and engagement. At the same time, it offered an opportunity for real-time study in the crucible of an ongoing pandemic. Not lost in this opportunity was the crying need for mental health care amid the isolation and social confinement the pandemic imposed. Ethical considerations abounded. Could one engage in research of patients in a time of heightened needs by the very same patients? Patrick Romani found an "unprecedented creativity and strength" by engaging a multidisciplinary group of colleague researchers in pediatric mental health. Innovative approaches to communicate with patients were resolved by working with the broader team. Such an approach met patient needs but also allowed clinical data collection to be used towards peer-to-peer reviewed research.

Conclusion

Maintaining the integrity of research remained central to our authors. Patient recruitment, staff risks of transmission, and asking for accelerated IRB approval were common challenges. However, scientists are by nature problem-solvers, and this is very precisely what our authors did.

What will be the legacy of the pandemic? This is the chapter that has yet to be written. Each of our researchers will take the lessons they learned and the insights they gained by overcoming their individual professional and research difficulties into the future with them. The flexibility and problem solving that the pandemic forced upon them can aid them in overcoming obstacles in the future. In this, they are not alone; their difficulties are a microcosm of what people of all age groups and professions in our greater society have faced this past year.

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Personal Narratives IRB Members and Research Administrators

Walter Dehority, Edith Paal, Stefanie E. Juell, Edward De Vos, Jennifer Randles, Brian Moore, Sara Griffin, Hallie Kassan, Sujatha Sridhar, John D Tupin, Ann Johnson, Joan B. Cobb Pettit, Gabrielle Rebillard, T. Howard Stone, Carol A. Pech, and Kebenei Enock Kipchirchir

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Therapeutic Misconception, Misestimation and COVID-19 Research

Walter Dehority

The first reports of a novel SARS coronavirus emerging from China in early January of this year did not capture my attention as they should have. This, I reasoned at the time, was a virus halfway around the world, probably an oddity of interest only to virologists in East Asia. I would soon learn, however, that this would evolve into a plague, the likes of which had not been seen in a generation. As inconceivable as it seemed at the time, this virus would eventually affect my work as an Institutional Review Board (IRB) chair in New Mexico. Warily, I watched as the virus entered Europe and the rest of the world. Soon, curiosity in the West transformed into worry, which rapidly gave way to terror. Images of over owing intensive care units in New York City filled my cellphone screen. Health care workers were forced to use garbage bags for protection after supplies of personal protective equipment (PPE) disappeared. Hospitals ran out of ventilators. (These equipment shortages can be seen documented on the CBS *60 Minutes* segment "Sick doctors, nurses and not enough equipment: NYC healthcare workers on the fight against the coronavirus.") Still, the virus moved further and further west from New York, eventually heading for my own borough.

I watched as panicked physicians, patients, and media outlets turned to the research community for answers, desperately hoping cures, vaccines, and preventive measures could be produced. Repurposed drugs and experimental agents with in vitro activity against the virus were rapidly identified. Small, uncontrolled studies began to appear in the literature, many bypassing peer review, feeding scraps of pilot data to a frightened medical community. Clinical trials materialized overnight, as the website 'ClinicalTrials.gov' exploded with hundreds of new COVID-19 studies. At the local level, our investigators, clinicians, hospital administrators, and the populace they served advocated for the initiation of clinical trials in our hospital. Researchers wished to contribute their expertise to help generate data. Administrators hoped to offer our hospital as a trial site for a number of coveted experimental therapies for the community, while patients were willing to volunteer for studies of these new treatments. From one perspective, such efforts were laudatory, and a remarkable demonstration of determination and altruism. From

another perspective, the clinical trials arising from these efforts would soon force me to confront the idea of therapeutic misconception and misestimation as never before.

Therapeutic misconception—as defined by Henderson, Churchill, Davis, et al. in the journal *PLOS Med*.—is the failure to appreciate the distinction between the goals of research, which are to collect data to contribute to scientific knowledge, and the goals of clinical medicine, which are to improve the health of patients. Pentz, White, Harvey, et al., in the journal *Cancer*, de ne therapeutic misestimation as the misestimation of the level of risk and chance of benefit in a clinical trial. As in other hospitals around the country, patients in our hospital wanted cures, and many were willing to be the recipients of untested drugs in their quest for such cures. This simple fact kept me awake many nights before an IRB meeting that Spring. Would any of our potential research subjects actually consider the warnings in a consent form about the possible risks and lack of proven benefit for an investigational therapy when offered the chance to participate in a COVID-19 clinical trial? Particularly after these potential study subjects had viewed the same images of death in New York that I had? For that matter, would our worried health care workers be able to objectively appraise the opportunity to participate in trials of preventive measures against the virus, such as vaccines and prophylactic drugs, after they had viewed the images of health care workers in New York using garbage bags as PPE? Internet and media sources continually promulgated a steady stream of real-time updates on seemingly every development in the ongoing search for a cure or a vaccine. No longer restricted to the esoteric domain of medical journals, major media outlets now trumpeted the results of clinical trials and obscure phase 1 studies with breath-taking abandon. Co-workers frequently stopped me in the hallways to ask if we would be a trial site for many of these proposed therapies or vaccines, a hidden glimmer of fear (and hope) in their stares. Hope may arise from fear, whether or not that hope is misguided. A drowning person will reach for any lifeline thrown their way, whether or not that line is secure. How could our IRB best ensure subjects would be able to make informed choices as to whether they should grab these experimental lifelines and not just reach for them blindly out of fear? Therapeutic misconception and misestimation, which I previously associated with the use of investigational therapies in early phase oncology trials, were now suddenly front-and-center and affecting our entire community.

Therapeutic misconception and misestimation do not just affect study subjects, however. During troubling times, as I learned, these thought processes may also affect IRB members (myself included). In my case, they assumed a different guise, which was harder to recognize, namely a self-imposed pressure to make experimental therapies rapidly available to our patients, and to quickly facilitate the opening of our hospital to clinical trials to do our part to aid a community (and nation) in crisis. Hindsight now permits an appraisal of the many ethical issues this raised (both locally at our hospital and nationally). These were issues that I did not adequately appreciate while in the throes of the pandemic's rst months. Many studies were, by necessity, hastily constructed and targeted critically ill patients who may have been most at risk of therapeutic misconception or misestimation, as well as worried health care providers looking for prophylactic medications as they entered the front lines in the fight against the virus. Given these concerns, did the medical community really need 104 trials of hydroxychloroquine that April (all presumably IRB approved, two from our institution), many of which were single-site, underpowered, or uncontrolled studies? (The number 104 was cited in an article by Dehorty, Spence, and Dinwiddie in the journal *Pediatric Allergy, Immunology, and Pulmonology*.) To better protect these study subjects, would waiting for the results of larger, well-designed, multi-site controlled trials have been wiser, allowing us to maximize scientific gain and minimize exposure of desperate subjects to risks borne out of fear?

Nonetheless, proposed trials kept appearing on our committees' agenda, though not without concerns. Did sufficient data exist to support an interventional trial at that point in time for many of these therapies? Were the hastily assembled study teams and data safety monitoring boards qualifie to conduct or adjudicate these studies? Were the

waivers of informed consent we granted for some single-arm therapy trials necessary (in intubated, critically ill patients whose families were not allowed into our increasingly locked-down hospital to provide consent)? Were such waivers acts of bene - cence, providing opportunities to receive potentially life-saving medications for those unable to request them, or attacks on those subjects' autonomy? Time for such deliberations was often sacrificed upon the altar of speed and efficienc . I sifted through preliminary data from studies in rodents and small, underpowered and uncontrolled trials, looking for kernels of hope that may suggest a new modality was ready for a proposed trial in humans, while over my shoulder, in my workplace, and in my home, the specter of COVID-19 grew ever larger, challenging my impartiality. At times, hope, influenced by therapeutic misestimation, may have prevailed over caution or scienti c reason in my mind. Such insight, more easily achieved after the fact, is difficult to rely upon when a pandemic finally reaches your borders and comes knocking on your door.

The difficult decisions and ethical balancing acts did not end with the approval of such research. Scientific data that could impact the conduct of these trials were being published daily. Studies, which several weeks prior we hurriedly approved during emergency IRB meetings, were now being hurriedly assessed for closure or suspension due to newly identified risks in the rapidly expanding medical literature. The perceived beneficence behind the initial decisions to approve such studies could quickly transform into an attempt to ensure non-malfeasance. Studies constructed to test the efficacy of the drug hydroxychloroquine came into question almost overnight following the publication of a study in the *Lancet*, demonstrating a potential increased risk of mortality with use of the drug. However, less than two weeks later, the same study was retracted by the journal. This left IRB's (including ours) to ponder the best course of action for their local hydroxychloroquine trials, and to wonder whether the original approval of these studies may have arisen, at least in part, from the influence of therapeutic misconception or misestimation.

Experience adjudicating emergency research in my role as an IRB chair was something I was lacking at the time COVID-19 arrived, which is perhaps why I continue to reflect on these events. I believe that during such challenging times, IRB's may find themselves caught in the middle. They have a genuine desire and responsibility to rapidly approve clinical trials that will facilitate the study of novel drugs, vaccines, and diagnostic modalities that may produce urgently needed data. However, in competition with this responsibility is an equally important need to slow down during what is a time of relative urgency and critically evaluate each proposed trial in order to ensure the protection of the human subjects enrolled within it, even if that means asking dif cult questions that may delay the start of a trial, or lead to disapproval or modificatio of a study. At the core of therapeutic misconception and misestimation is an understanding that interventions with proven clinical benefit do not need clinical trials. Interventions without proven benefit do. It is those interventions that may either help or harm our study subjects. Adjudicating and evaluating clinical trials during a rapidly evolving pandemic, when hope and fear are present at all levels of the research community, is a challenge to which IRB's must adjust. Perhaps, I now realize, it is during such demanding times that the research subjects we work so hard to protect actually need us the most.

Eight Seconds of Panic

Edith Paal

Little daily emergencies are common in IRB offices. The one that hit our IRB office the week ending Friday, March 13, 2020 (of course a Friday the 13th was involved, right?) quickly evolved from a "little emergency" to something requiring an urgent rethinking of the full scope of our human subject research program and its oversight.

Our standard practice, when emergencies hit, is to allow ourselves about 8 seconds to panic. Then,

once that's out of our system, we settle in and work through whatever the day's issue is.

COVID-19 week, as we fondly think of it, would have merited a bit more than 8 seconds of initial panic, we know now, given the extent of the adaptations we have made since then. That was the week it became clear COVID-19's spread in our state was not a one-and-done kind of thing, that it would linger for weeks, if not months, and we had no choice but to deal with it. The entire campus, including the IRB office, had to rethink its functioning. My calendar for that week shows our IRB executive committee met Wednesday, March 11th. I remember joking that day about whether our meeting room was big enough for us to stay the recommended 6 feet apart from each other. I also know that was the last in-person meeting I had on campus.

Decisions needed to be made quickly. By Thursday, our eight-person IRB staff had chosen to immediately transition to working exclusively from home—decision number 1. Remember the days when things like virtual meetings and Zoom calls were a bit of a mystery? Well, they were to us at that time, and we knew they'd be a much bigger mystery to our IRB committee members, who had met in the same on-campus room every Tuesday afternoon for years. So decision number 2 was to cancel the next Tuesday's meeting to give us time to get everybody trained on an online meeting platform. Luckily, that looming agenda was short, and contained nothing too time-sensitive, so cancelling could be done without too much pain.

We spent the next seven workdays, and parts of some evenings and the weekends, trying different virtual meeting platforms. We had to consider cost for the features we needed and whether our institution had a license for the products under review. We video-called each other repeatedly, and we're not too proud to admit some of us asked our tech-savvy children for guidance on the various options. We chose one platform, trained our next week's IRB members on it, and had it up and running in time for the following Tuesday's meeting. We set up training meetings each week for the following week's committee members. We also used it for our daily remote staff meetings. And all of this was going on while we maintained the rest of our regular workload—processing submissions and getting things approved, responding to research team queries, and working on whatever big projects we always seem to be a part of.

The next emergency in the series was working through the decision of what sort of research should be allowed during the pandemic. We are the IRB for an academic medical center, and the University never closes, as our employee handbook reminds us. But it did have to scale back some activities, such as elective medical procedures, as the institution sorted out issues such as availability of PPE for clinical staff, clinic space, and whether personnel, including research staff, would be diverted to screening the public and institution employees for COVID-19 (they were).

Tough decisions had to be made. Our institution does all kinds of human subject studies—clinical trials of investigational drugs and devices; social-behavioral interventions; studies where study activities are done in the clinic, or the operating room, or the pathology lab, or the community, or in focus groups, or via paper and online surveys. These research characteristics affect each study's risks and benefits. Institution leaders were called upon to implement guidelines about what kind of research could continue, and what had to be put on hold. Research with the potential to provide direct benefit to subjects, such as treatment studies carried out when the subject would be in clinic for routine care, or studies that could be carried out virtually, were allowed to continue. Studies that required in-person contact, with little or no prospect of direct benefit, we e temporarily stopped.

The IRB fi lded many, many queries about what types of research could and couldn't continue. However, these decisions were made at the institutional level, not by the IRB. All we could do for the anxious research community was to direct investigators to the institutional guidance, and to review submissions for those studies that were allowed to start or to continue, with an eye toward assessing a new type of subject and staff safety risk—minimizing the risk of COVID-19 transmission.

Then came all the real emergencies for the entire institution—reviewing (and approving the use of) emergency investigational new drugs (eINDs) for COVID-19 patients, getting time-sensitive COVID-19 research studies up and running, and drafting from scratch an expanded access protocol for one

experimental COVID-19 treatment. Luckily, we found our clinical staff to be very appreciative of our explanations of the various steps that needed to be completed; we did a lot of handholding regarding the various submission requirements, both to the IRB and the FDA. (Box 10b on FDA form 3926, the one requesting the ability to use "Alternative IRB Review Procedures," is your best friend here, everybody!) Patience and willingness to go the extra mile to help our clinicians went a long way. Many had no research experience, so IRB and FDA submissions were new to them.

We are especially proud of the creation and approval of our expanded access protocol. The institution's Office of Research Regulatory Affairs worked Herculean hours drafting a protocol and consent form, including taking into account the potentially vulnerable populations (prisoners and non-English speakers) likely to be encountered in the target population. They got translators lined up. They dealt with the FDA. They got the whole submission prepared and ready to go, and then asked how quickly it could undergo IRB review.

Weekly IRB meetings seem pretty frequent, until it's Wednesday morning, you've got an expanded access protocol addressing a critical need, and your next meeting isn't until the following Tuesday. One of the big issues in setting up irregular IRB meetings on short notice was the difficulty of finding a meeting space and getting enough people to create an appropriately constituted IRB into said space all at the same time. That's when our newly developed expertise in online meetings saved the day. We selected appropriately qualified IRB members from our roster, gave them a call, and got enough of them to commit to logging on at the specified time to constitute a quorum. Our office staff then got to work creating a roster and getting the IRB registered as our ad hoc IRB with the Of ce for Human Research Protections before the meeting took place. Yes, those reviewers were a little surprised to learn that by agreeing to this meeting, they got themselves on the permanent roster for an ad hoc committee. They were reassured by our telling them that they would convene only in the case of things like emergency uses or other circumstances requiring immediate review, and that a PI missing a submission deadline would *not* be considered an emergency.

When we first switched to the all-remote working and meetings, we were told it would be at least the end of May before things returned to normal. Well, here we are in the middle of October, as this is written, and we're beginning to think remote work and meetings will be our new normal. Daily IRB office staff meetings keep us connected with each other. Our reviewers seem happy to not have to take the time to come to our meeting space. Online meetings also make it easier for us to include far-flung consultants with special expertise. We're still getting used to the slight time delays in virtual meetings, but we're enjoying the unexpected cameos by reviewers' children and pets.

As an added bit of spice, all of this was going on while we were in the middle of preparing our reaccreditation application, due to the Association for the Accreditation of Human Research Protection Programs (AAHRPP) by mid-September. Accreditation standards got us thinking about the lessons learned from this experience. We were thrilled to have successfully navigated the COVID-19 challenges so well during a time when it felt like we were all flying by the collective seat of our pants. Now that the mayhem has died down, a little, we plan to give some thought to developing and documenting a more organized plan for responding to events that force an immediate rethinking and adaptation of our human subject research program and oversight. While we think we're doing OK by allowing ourselves only 8 seconds to panic before digging in, maybe formalizing a plan will allow us to cut that to 5 or fewer seconds in the future.

IRB Work During a Pandemic: Remember Your Values

Stefanie E. Juell

During the first and second week of March 2020, my department director and I spent hours in meetings. Not only were we grappling with our own personal fears and uncertainties as the COVID-19 pandemic continued to spread

across the globe but we were also attempting to define the limits of our ethical obligations to our staff, our institution, and our community. We knew that our entire department was able to function remotely. At the same time, higher-level leadership was reluctant to permit such a dramatic shift, especially when some employees were not able to work remotely. But with each passing day in early March, my office was increasingly inhabited by staff members on the verge of tears. Some even considered quitting because these (mostly women) truly felt their lives were at stake for the purpose of being physically present in the office

Our department forms the core of the Human Research Protection Program (HRPP) within one of the hardest hit hospitals and academic medical centers in New York City. Ninety-five percent of the research we oversee is biomedical. We work with populations diagnosed with diabetes, asthma, cancer, HIV, substance abuse disorders, and addiction among others, and manage trials involving investigational drugs and devices funded by federal grants, industry sponsors, and internal funds. Many of our patients are some of the most vulnerable: families living at or below the federal poverty line, undocumented individuals, families without easy access to fresh, nutritious food, and communities struggling with systemic racism and *severe* financia stressors.

New York City residents not only live on top of one another; we also work on top of one another. Our staff share small spaces, and many of these spaces have no windows. Our staff rides subways and public buses to get to work and, in doing so, share tight spaces with hundreds of people.

We HRPP folks are compliant by nature. We want to do the right thing. And we want to follow the rules and the laws. We spend our days explaining to other people how to follow those laws while also upholding ethical principles that sometimes extend beyond the minimum requirements speci ed in the regulations. When the pandemic's arrival in NYC had been confirmed on March 1st, and as this virus spread like wildfi e throughout our metropolitan area, no dilemma was more pronounced for me than the tension between "following the rules" and "doing the right thing." Expectation and responsibility; law and ethics; written law and the intent of such laws. And to whom did I owe my loyalty? The organization as a whole that expected me to remain physically present at work? Or to my staff who couldn't focus on their work because of their rapidly deteriorating emotional states and increasing stress levels?

On Thursday, March 12th, shortly after another conversation during which my director and I questioned whether we could, as managers, ethically continue to require our staff to be physically present, I stood alone in my office distractedly eyeing my plants to determine which I would let die. I assumed I would not be back for quite some time and couldn't carry them all home. I left that evening and, fortunately, was informed by our organization's leadership the following Monday that remote work was now permissible for those able to perform their job duties from home. I felt a sigh of relief that earlier that week, New York City had issued guidelines asking citizens to avoid densely packed subways, buses, and trains, and that the governor had closed state and city colleges and universities. Suddenly, the decision-making had shifted to the state and the city. I no longer felt responsible, as a supervisor, for putting people at risk.

The next several months were, by far, the most challenging period in my professional career. Between March and June, our entire department worked seven days per week, often 10–12 hours per day and late into the evenings. Prior to the pandemic, only about half of our staff worked directly as IRB staff. During this period the number of staff required to complete IRB related work doubled—every person in our department was doing direct IRB work. And even in doubling the number of individuals engaged in IRB work, we still could not function without working seven days per week.

We quickly adapted. All of our in-person IRB meetings quickly shifted to Zoom, as did all of our standard staff meetings, and one-on-one check-ins. It was difficult to concentrate during those Zoom calls because conversations were often cut off by ambulance sirens, which sped by every few minutes. And it was hard to focus knowing what each

of those sirens represented. We were inundated by emergency use requests by clinicians who had no prior experience navigating FDA regulations. Some of those requests came from small, unaf liated community hospitals with no experience in research whatsoever but desperate to offer their patients some form of treatment. Our staff monitored the IRB inbox constantly. We promptly responded to pandemic-related emergencies—and many of these conversations with clinicians happened on weekends or after dinner, some as late as 11 PM. No one actually asked us to work these hours. But even though we weren't frontline healthcare workers, we all understood that our ability to quickly respond to questions from clinicians about the use of non-approved drugs might very well be the difference between life and death for patients in need of such treatments. I felt personally responsible for the lives of patients I never saw.

In addition to the urgent questions, the IRB was also flooded with questions regarding continuation of research (was it allowed?), amendments to the consent process (unnecessary risk of exposure to request written consent), questions about Legally Authorized Representatives and proxy consent (family members were no longer allowed in our hospitals). Were amendments required for all of these consent changes? What about protocol amendments for switching from in-person to remote visits? Did sponsors need to be notified? Contracts amended as well? What about FDA-regulated studies that required signatures? And HIPAA Authorizations? How could we handle this volume of amendments coming in?

We decided fairly early on that the only way our IRB could manage to function was to prioritize the true emergencies and to adapt our processes for the minimal risk, less substantive changes. We created a shorter COVID amendment form rather than requiring researchers to follow our standard amendment process. And we issued guidelines prospectively allowing certain categories of changes (such as switching to remote visits for minimal risk research whenever possible) without immediately informing the IRB and instead requiring that summaries of those changes be submitted at the time of continuing review. We continued to require standard amendments for changes related to documentation of informed consent because there was no way out of this for greater than minimal risk FDA-regulated studies. We also created a running list of research pandemic FAQs that all of our staff contributed to as questions came in, and we posted our responses to those questions on our website for the entire research community. And, since even the most senior of our staff (I have ten years of experience in this field) were faced with questions that pushed us well beyond anything our expertise and experience could have prepared us for, we scheduled meetings just to determine appropriate, permissible, and consistent responses to the questions we received.

Emergency use requests do not require IRB review or approval, and so we very quickly figu ed out that we should set our email auto-replies to provide full instructions for clinicians who needed FDA approval on emergency use requests. Other urgent questions surrounded clinical trials—access to trials, opening of trials, IRB review of trials, coordination with other research administration offices Most trials take weeks or even months to open, and most of our greater than minimal risk research took about a month to review at the IRB. Suddenly we were being asked by our uppermost leadership to convene full board meetings within a day.

And those full board meetings were no less challenging than the situation we found ourselves in on a daily basis. Our Board members and IRB staff were exhausted, scared, frustrated, overworked, and overwhelmed. Our conference rooms had been turned into hospital rooms. The library had been turned into a medical storage facility. Clinicians were working overtime all the time and trying to catch naps on chairs. And our frontline healthcare workers were getting sick. Some passed away.

All of our HRPP staff are also IRB members. Many are ethicists but most are not scientists. I vividly recall a prospective hydroxychloroquine trial that was being proposed at our facilities. I, not being a clinical expert, expressed concern that there was insufficient evidence in the protocol to convince me that the benefits outweighed the risks associated with the drug, especially for participants

with cardiac conditions. I was promptly and publicly shamed and questioned by a scientific board member who snapped, "Isn't that exactly what we're trying to figu e out!?" I may have been the only person on the Board that day to vote against the study. We have since seen that the FDA revoked the Emergency Use Authorization for hydroxychloroquine. As a non-scientific "staff" member of the IRB, speaking up about my concern and subsequently being shamed for asking such a question took courage and strength. I didn't take it personally because I could recognize that the frustration was coming from a place of desperation in this individual Board member. But as an IRB member, an HRPP administrator, and an individual who possesses degrees in ethics and philosophy, I could not allow myself to succumb to the pressure of desperation. I had to stick to what I knew. That no matter the situation, pandemic or not, decisions about the approval of clinical research had to depend on sound science, minimization of risks, appropriate inclusion-exclusion criteria, and detailed and careful planning for recruitment and data safety monitoring. Equally important was the IRB's ability to make decisions independent from any political pressures from the institution or the research community. The IRB's purpose is not to impede research. As my coworker says, "The IRB likes research, too." And we are also quite good at understanding the perspective of many stakeholders. We think carefully and critically about the stages of each clinical trial and we are quite skilled at determining in advance what might possibly go wrong. We take our jobs seriously, both board members and staff, and we care most about doing the right thing in the right manner.

So what advice do I have for IRB members and staff? Maintain confidence in what you know. Adhere to the principles that have always been a guide for your work. And, most important, remember the fundamental purpose for your existence: to protect the rights and welfare of research participants. Pandemic work, for which none of us were prepared, requires flexibility and creativity in terms of meeting regulatory requirements but it is crucial to remember that the regulations themselves serve a larger purpose. We have a duty to approve sound science that is based on an assessment of submitted materials—not based on political pressures or even external circumstances. It's often during those times that we feel most pressured to move quickly that we actually need to slow down.

Take time to assess current staffing levels. Act as a leader and delegate specific tasks to specific individuals. There's a reason we are taught in CPR certification courses to look a person in the eye and ask that individual to call 911 while we administer CPR. Specific assignments help the work get done and allow individuals to actively focus on something helpful. It's easy to become paralyzed by indecision during a pandemic.

For IRBs specificall , make sure your responses are consistent. Determine flexibilities in the regulations that can allow you to reduce the number of individual submissions coming in. Publish publicly available guidelines. And make sure your Board is comprised of non-scientists and non-clinicians who are available and willing to speak up. Include the community members in every meeting, and onboard more of them. Ask them to speak up and give them an active role by asking them to serve as secondary reviewers.

Stay mindful of the human element. Recognize the invisible work being done and call it out. Give credit where credit is due. Choose phone calls or video calls over emails or text messages. Listen. Validate. Recognize that everyone is struggling and recognize that some of us may be struggling more than others. Be mindful of your own mental and physical health and set boundaries to attend to your health. Rest, sleep, diet, exercise, laughter and time outside are basic requirements for our species yet we often ignore these basics, which only damages our health and the quality of our relationships and interactions with others. We must remember that businesses function because of people. And people are not machines. Having emotions isn't unprofessional. It's human. And the emotional, psychological, physical, and financial impacts of a pandemic must not be ignored with the expectation that we will seamlessly carry on business as usual. Pandemics don't last forever, and we owe it to ourselves, our colleagues, our families, and our communities

not to forget the values and principles that tie us together and define who we a e.

Ethical PPE: Overseeing Research in the Time of COVID-19

Edward De Vos

As many in a weary nation look toward science for insights, answers, and a path out of this modern plague, science itself runs the risk of exposure and illness. Since the end of World War II, the *Nuremberg Code* (1947), the *Declaration of Geneva* (1948), the *Helsinki Declaration* (1964), the *Belmont Report* (1978) and its codification in the *Common Rule* in the U.S. Code of Federal Regulations represent serious efforts to protect participants in human subjects research from risks associated with their participation.

In research settings, whether university-, hospital-, or industry-based, it is the Institutional Review Board (IRB) or Human Subjects Committee that is charged with overseeing an institution's human protections program and compliance with regulations. This includes assuring that key research personnel have successfully completed training programs on protecting human subjects from research risks, reviewing research protocols in accordance with federal regulations and criteria, providing feedback and approvals to researchers before implementing protocols, overseeing the proper execution of the research, responding to requests for amendments prior to their implementation, and investigating unanticipated problems and adverse events that may occur despite the best of intentions.

Research is difficult, both theoretically and practically. While the practice of ethical research is grounded in legal regulations, the ethics themselves are rooted in normative values and a more universal moral imperative. Translating this code into practical operations can be a tricky affair. Some very challenging protocols require what verges on Solomonic wisdom to render a decision. Thankfully, most protocols are not that challenging. And many, historically, have carried no more than minimal risk, often defined as the risk associated with day to-day life.

Yet as COVID-19 captures headlines and the media report daily new case counts and deaths with the fervor of sports fans following their playoff-bound team or investors following the stock market, the risks associated with daily life have changed radically. COVID-19 is not only an important subject of study, but it has affected the context within which research is conducted, and the risk environment within which IRBs must deliberate.

It is within this broader context that I received NIB's survey on COVID-19 and its impact on IRBs. The survey provided an opportunity to reflect and sort out some of the challenges I experienced as an IRB Chairperson, and the efforts we undertook to address them. This personal story shares some of those challenges and what we've learned thus far as well as some emerging dilemmas as the pandemic continues.

The first challenge is a logistical challenge associated with review and oversight of COVID-19 research. This is less a matter of "COVID-19 Research," per se, but accommodations to previously approved protocols that involved face-to-face interviews. These were protocols that were approved before we were even aware of COVID-19 and prior to widespread mitigation efforts, at the state level or nationally. I reached out to all Principal Investigators (PIs) of active protocols requiring amendments if they were still actively engaged in recruitment and/or interviewing. I created a streamlined application process that outlined the required changes (to informed consent, recruitment materials, and the addition of screening questions to online interview protocols), and requested current information on the status of recruitment, interviews completed, and interviews still to be conducted. This resulted in a spike of amendments to be processed, but the streamlined procedures facilitated administration.

The next challenge involved ethical, regulatory, or institutional policy challenges or concerns.

Online interviewing carries additional risks and responsibilities. *Both* the researcher as well as the participant must be able to identify spaces to conduct the interview in which they are unlikely to be observed, overheard or interrupted. Except for those living alone or those with privileged amounts of space, this can pose a challenge. Nevertheless, for much behavioral research, where a breach of confidentiality may be the greatest risk attached to participation, the need to maintain privacy is critically important. In addition to modifying the informed consent documents to stipulate that privacy, the interview protocols must add screening questions regarding the physical setup within which the e-interview will be conducted. This begs a separate question about cybersecurity and the privacy afforded by varying e-platforms. This remains a concern.

Among the *Belmont Report*'s three fundamental ethical principles is *Justice*, which concerns the equitable distribution of risks and benefits among participants. While researchers may seek to broaden their pool of participants to gain greater diversity and potential generalizability (and, should the results warrant, utility), the demands of online research may pose challenges to inclusion of more diverse populations. Historically underserved and marginalized populations are disproportionately represented among the poor, and poverty may limit the ability of some to participate in online research. Internet access, bandwidth, and equipment capacity may pose obstacles.

Previously, I described the extra efforts needed to secure confidentiality to minimize risks in accordance with the *Belmont Report*'s principle of *Beneficence*. Here too, however, poverty, through its effects on affordable housing and population density, may make it difficult for would be participants to secure the space and privacy required for confidential online interviews as stipulated by the informed consent as required by the approved protocol.

As the COVID-19 pandemic continues, we must weigh the need for temporary accommodations versus long term sustainable solutions. If in the short term we assign higher priority to minimizing risk, we risk paying less attention to equitable distribution of burden and benefit. As the pandemic continues, we must seek alternative ways to counteract the disproportionate medical and economic impact the disease has on the poor and people of color, and to identify feasible ways to promote and secure their involvement in research. Without those efforts, we run the risk of turning back the clock on research's effort to diversify the knowledgebase, and with it, secure benefits for all segments of the population.

Finally, I offer general advice to IRBs and researchers during this pandemic, whether they are directly studying COVID-19 or not. While physical contact, viral spread, illness and death must be the top priorities, I urge IRBs not to overlook the implications of moving to electronic platforms for conducting other forms of research. In most instances, the researcher will be unable to control their participant's environment. As such, increased attention must be given to maintaining the confidentiality of the interview through informed consent attestations, and through the addition of screening questions within the interview protocol itself. Longer term, attention must be given to alternative models to secure more diverse participation, which will secure added benefits for those who have historically born disproportionate risk for so long.

Navigating the Ethics of a Crisis

Jennifer Randles

I vividly recall Friday, March 13th, 2020. It was an unseasonably warm, sunny day in Central California, and though I did not know it at the time, my last working day on campus for the foreseeable future. I attended several meetings that day related to my various roles—study principal investigator, faculty, Sociology Department Chair, and Chair of our University IRB, the Committee for the Protection of Human Subjects. Just two days earlier, I held my final in-person class meetings

with my students as we discussed the University's announcement that we would transition to fully virtual teaching and learning the following Monday. We knew very little about COVID-19 in mid-March 2020, but experts were already predicting the vast human toll of the pandemic and related economic recession. I wept as my students and I discussed the suffering that would likely ensue, not just for those physically affected by the virus, but also for those who would lose their jobs, access to basic needs, and life-sustaining connections to others.

In the last few work hours of that Friday afternoon before I unknowingly picked up my four-year-old daughter from daycare for the final time, I perused the Centers for Disease Control and Prevention website for guidelines about the use of personal protective equipment, physical distancing, and heightened COVID-19 risks to older and immunocompromised groups. There was no way I could have envisioned this turn merely seven months earlier when I started my first term as University IRB chair. For almost 20 years prior, I had conducted ethnographic research on families in poverty and taught qualitative research methods courses. These courses always included a detailed section on research ethics and an historical overview of egregious ethical violations like those in the Tuskegee Syphilis study in which human subjects were treated much more as *subject* and much less as *human*. This was a crucial foundation, but it did not fully prepare me to enter the world of IRB administration. COVID-19 hit just as I was starting to get a handle on the details of my university's IRB policies and procedures and figuring out how best to explain risk designations and review categories to faculty PIs and oversee numerous departmental and unit IRBs. After attending several IRB bootcamps, trainings, and webinars the previous semester, I quickly learned that the IRB admin world was more complex than I had ever imagined, requiring nuanced and professionalized knowledge, not only about research, but federal regulations and creating a culture of compliance.

My entrée point into this world, one I would come to see as a unique institutional realm with its own customs, norms, and language, was one of sociologist and researcher, not IRB administrative professional. I was fortunate to have had wholly positive experiences as a student collaborator and faculty principal investigator with various IRBs, and I regarded their work as crucial in facilitating ethical research. I quickly learned just how many faculty experienced IRBs as a dreaded but necessary institutional hoop through which to jump, a potential obstruction to conducting research on which their professional reputation, tenure and promotion, and students' progress through degree programs depended. With one foot still deeply embedded in that world, I knew faculty were now facing unprecedented challenges of suspending in-person research and transitioning to virtual teaching, all while facing shelter-in-place restrictions that prompted daycare and school closures and the end of social life as we previously knew it.

Our prior understandings of risk and vulnerability were being shaken to the core. There was an expected uptick in modification requests from PIs who quickly pivoted their research to virtual data collection and those who devised new research projects to study the various and far-reaching impacts of COVID-19. Not only did the pandemic necessitate research redesign, it also required researchers to reassess the unique physical, psychological, emotional, social, and identity risks to human subjects. Researchers have since found themselves in a dilemma: these risks were and still are largely unknown, but we need well-designed, ethical research to identify and understand them. We are quickly establishing a solid knowledge base about "high-risk" groups from a bio-medical perspective, those who due to pre-existing health conditions, age, sex, and race are more likely to develop serious, life-threatening cases of COVID-19. But we are slower to understand social-behavioral risks, such as our country's deeply rooted history of structural racism that results in greater job loss, lower wages, and a higher likelihood of complications and death after contracting COVID-19 for people of color.

The pandemic has created new vulnerabilities and thus requires a distinct risk-benefit analysis: what are the risks of studying populations disproportionately affected by COVID-19? What are the

risks of not studying them? As with so many things right now, we are both rapidly adjusting to a quickly moving target, while feeling as though we are at a standstill. We must continue to reassess the fundamental question: what are the ethical implications of continuing in-person research and studying the impacts of the pandemic *during* the era of COVID-19? Add to this the challenge of not knowing when and if an endpoint is in sight. It is very likely that we are never to return to the "normal" we last knew on that Friday in March. Some people are seriously pressed for time right now, struggling to balance the competing demands of paid work, unpaid caregiving responsibilities, and the mental and physical challenges of living through a societal crisis. What are we asking of them when we ask them to participate in research? Others are facing unprecedented loneliness, social isolation, and a loosening of the structures that once dictated predictable rhythms of daily life. How do we develop rapport when we must practically remain six feet apart, our facial expressions covered, every trace of our presence soon wiped away by the disinfectants that could save a life? These are not conditions conducive to establishing meaningful human connections. We are social beings primed for empathy and compassion, and we feel the collective stress and strain of the pandemic, even if our lived experiences are steps removed from its worst outcomes. This sense of social strain comes through in my conversations with PIs, many of whom worry about the ability to start or continue research projects many months or even years in the works.

I personally got no fewer than 10 requests to participate in research on how employed parents and caregivers were coping with the dual challenges of essential in-person work or working remotely at home while homeschooling and providing 24/7 childcare. Most of these PIs were employed mothers who had worked quickly to submit IRB applications proposing studies on the real-time constraints imposed by COVID-19 restrictions, all while they were being pushed to the brink at home themselves as the already thin lines between work and home blurred even more. I feel this acutely in my own life. Our April 2020 IRB meeting involved me trying to maintain my composure while my young daughter tickled my feet for 20 minutes. Since March, I have written most IRB decision memos between 4:00–6:00 a.m. because those are the only two truly quiet hours in my workday now. I had to significantly curtail my own involvement in the one study on academic mothers in which I agreed to participate because I could not find the time to log my daily activities, and journaling about the experience triggered extreme feelings of guilt, exhaustion, and resentment. Preliminary research is already revealing that women's academic journal submission rates are down, along with their paid work hours and sense of well-being. The pandemic is reinforcing deeply entrenched research inequalities and will likely have long-lasting scientific ramifications for decades to come.

It also presents an opportunity to consider the benefits, risks, and tradeoffs of virtual data collection. Most of the research I conduct and review is social-behavioral. My current research project on parents' experiences of diaper need—not being able to access sufficient diapers—involves telephone interviews. The drawbacks are loss of contextual data, such as missing nonverbal cues and expressions. But it also enables me to expand the geographical reach of data collection and generate greater respondent comfort and rapport, a key consideration given that I interview marginalized mothers about sensitive topics, including poverty and struggles to provide for their children's basic needs. Moments of needing to put down the phone, often to care for children, are aided by the conversational nature of the phone call and the fact that the research encounter is neither in their homes nor in a space I control, like my office. I went into the pandemic not assuming that virtual data collection was necessarily inferior and knowing that it could potentially mitigate risks of a palpable power imbalance.

For all these reasons and many others, it is a particularly challenging—and meaningful—time to be an IRB administrator. We are living through an unprecedented period when the collective sense of grief, exhaustion, and being unmoored presents a new set of ethical considerations involving the lives of those who review, conduct, and participate in research. In the end, I truly believe that the core

principles of ethical research can guide us along a path to coping with these challenges and facing the daily dilemmas of the COVID-19 era. Should we resume in-person instruction? Should we get together with friends and family? Should we continue our research agendas, and if so, how? We can find guidance in the fundamental principles of human subjects research ethics: minimizing risks, maximizing benefits, seeking truly informed consent, ensuring scienti cally sound decision-making, avoiding prejudicial assumptions about others, and especially protecting the most vulnerable among us. These are not only the guiding principles of IRB administrators. Respect for personhood, beneficence, and justice are collective promises that reflect our core humanity. As such, they are the best guide for how to navigate this crisis—in our IRB offices, our classrooms, our research encounters, our homes, and our relationships with one another.

IRB Members Perspective During COVID-19

Brian Moore

March—Week One

Our weekly staff meeting comes to a close. Some people linger for study—they have specific questions, while the remainder pack up their legal pads and spiral notebooks before retreating to their offices. There was some rumor of remote work and some vague plans discussed but with the assurance that ample time would be provided to make alternative accommodations. Little did we know that a week later most in-person research would be shut down and a wrench thrown in the finely tuned cogs of our infrast ucture.

March—Week Two

Despite a carefully worded and comprehensive message to the research community my email box is bursting and my phone, forwarded to my personal number, rings non-stop. It is often stated in professional circles that each study is different and must be handled based according to the nuances and details of the particular trial. This is never truer than trying to fit all the different shaped pegs into the round holes of the regulations. Some studies fit smoothly. To the disgust of investigators, some will not fit no matter how hard we try. Most are able to be re-shaped to fit the regulatory requirements and the needs of the researchers within the restrictions placed by the institution. The most common questions revolve around what alternatives are available regarding the process of informed consent, and continued research visits through a remote process.

We completed a 100% virtual IRB meeting today. This has only been used for inclement weather situations in the past, but will soon become the new normal. The board members are patient and open to the new format. The discussion and vote are consistent with our in-person meetings, so we adjourn satisfied that although not sitting side-by-side, we have fulfilled out ethical, moral, and regulatory obligations. Several members who are either unaffiliated with the organization or located in an outlying clinic location previously participated in the meetings remotely. This approach has proven invaluable for having the resources already in place for a more long-term plan.

May—Week Seven

Most in-person research activity is still shut down but that doesn't mean that continuing review expiration dates can be extended. Many new COVID-19 related trials are being submitted. There is some degree of urgency for these submissions, however, the established process of review, discussion, and documentation is upheld. Sometimes COVID-19 trials are triaged to be assigned for review ahead of others, but we don't take any shortcuts or skirt any corners of the regulations. We have implemented a platform to compliantly document electronic signatures for informed consent documents. This was probably overdue, but the use case was very compelling and is of great assistance to our investigators in terms of both compliance, and practicality

in obtaining and documenting the informed consent process.

The IRB staff have been working remotely for six weeks. There are still some technical issues and limitations. Communication is good and with some creative work-arounds we are able to maintain our normal meeting schedule and near-normal times for approval. There have been personal challenges regarding remote education for my children. These types of challenges have forced many of us to flex our work hours to fulfill the needs of multiple groups, while also supporting the IRB members and researchers in a time of crisis.

September—Month Six

We are six months in to a long journey. At the beginning of the COVID-19 outbreak, I reminded our staff that this was going to be a marathon, to not burn-out or expect everything to magically return to the "old normal" overnight. Periodically, through the process, I have told them that we are on mile 2 of the 26.2 mile marathon. They rolled their eyes, but at this juncture there is no immediate change in sight. However, there are many lessons learned and reflections on things that both went well and things that can be improved.

The Good

1. IRB meeting formats had to be changed, but the cadence of meetings was sustainable.
2. Having a list of readily available alternates was helpful for establishing quorum for the meetings as everyone's time is even more precious than before.
3. Significant amounts of education have taken place. Whether on the different options for obtaining consent or collecting data during adverse situations, researchers and IRB members were forced to think critically and make a careful evaluation of what is required by the regulations versus what is the institutional preference of normally doing things.
4. New technology and alternative methods were instituted that made research during the time of the pandemic more feasible and may help for planning of future studies as well.

The Bad

1. The initial reactions and sudden need for alternative arrangements shone a light on many areas of weakness. Just as children practice the fi e drill in their school, institutions and IRBs can learn and practice for future events. Having a disaster plan and periodically testing remote work capabilities would be prudent in the future.
2. Work-life balance has been a struggle for many individuals, due to lack of childcare, school closings, remote education, and caring for loved ones. These situations have forced us to be more adaptive throughout the day.

At the end of the day, the IRB and researchers at our organization have similar objectives—to promote the safe and respectful conduct of high-quality research. Each party has a different perspective, and sometimes timelines differ, but the underlying concepts of respect, justice, and beneficence have shown through. Researchers and IRB reviewers now have a greater appreciation for what is best and safest for study participants and how to be flexible in accommodating their needs.

Editor's Note. This story complements Rebecca Erwin Wells' story, which is included among the researcher stories in this symposium.

Research on COVID-19: Stories from IRB Members, Research Administrators, & Investigators

Sara Griffi

From my perspective, as both an IRB staff member and IRB Committee member, the COVID-19 pandemic brought to light many opportunities for improvement and better collaboration in the review of human subject research (HSR). In my experience, the pandemic exacerbated issues that commonly arise in the review of HSR,

and it also brought challenges that were previously unanticipated. This re ection rst focuses on the issues I experienced as an IRB staff member along with the remedies to those issues and then pivots to my experiences as an IRB member. I hope that this re ection will serve as a comfort to those who experienced similar issues and perhaps felt isolated in the struggle and as an aid for those still struggling to navigate the review of research during this time.

A key aspect of my role within the IRB Of ce is to assist teams with the consent process and manage the research consent form templates utilized at the institution. Pre-pandemic, I would often receive requests to ease consent restrictions within a project even though the project did not even meet the regulatory requirements for a waiver of consent or documentation of consent. While I could often sympathize with research teams seeking to lessen the burden of a lengthy consent process on subjects, these requests could generally be denied without ill consequences to subjects or the feeling that a disservice has been done. In the case of the pandemic, however, there was a strong desire on the part of both researcher and IRB staff to allow as much exibility as possible due to the unprecedented nature of the pandemic restrictions and the potential risks involved in consenting subjects in person. While some exibility was possible, it quickly became clear that there were many consenting options that would simply not be possible for the foreseeable future due to regulatory restrictions and institutional barriers. Most of the exibility that has been granted during the pandemic is applicable only to COVID-related populations. While this is understandable and appreciated, researchers who continue to conduct research in non-COVID populations have been left with few options. The issues relating to consent during the pandemic that have arisen ignited a number of institutional departments to pursue electronic consent options for FDA-regulated projects, but since this was reactionary, a signi cant amount of time passed during the pandemic in which researchers could not utilize electronic consent for research. This resulted in a continued barrier to conducting certain types of research and a feeling of helplessness on the part of IRB staff.

Another pain point at the outset of the pandemic was that the pace of communication within the larger Human Research Protection Program was not keeping up with the swiftness of change. Given the pandemic's impact on in-person interactions, one of my duties as the consent analyst within the IRB Office was to release and maintain guidance for consenting subjects during the pandemic. After spending numerous hours strategizing and studying the regulatory guidance on the consent process, it was a welcome relief to release the requested guidance. Only a few days after release, however, it came to my attention that revised hospital policies did not align with the main consent process highlighted in the guidance and recommended by the IRB Office. Not only was it slightly embarrassing to have been left out of hospital policy notification, but it also presented yet another limitation on how consent could be obtained and documented. Although this example alone was not the driving force behind the formation of a multi-institution committee that kept abreast of all COVID-related changes, this committee's formation did alleviate this recognized pain point and prevented situations similar to the one described above from occurring.

The difficulties and remedies described thus far in this reflection stemmed from my experiences as an IRB staff member, but I also experienced a set of different challenges while reviewing research as an IRB member.

Most of the dilemmas I faced while reviewing COVID-related research can be attributed to the seemingly endless review of overlapping research. Due to the pace at which everyone was moving at the outset of the pandemic, it was difficult to know whether or not someone at an institutional level was monitoring the number of projects proposing to recruit the exact same subject population. It was also troublesome to see a large number of separate projects seeking to collect and store data and biospecimens for future unspecified research. While these concerns reflected issues beyond IRB purview, the fact that the IRB could be the only entity witnessing this disorganization concerned me. Thankfully,

these issues were short-lived and occurred very early in the pandemic. Partly due to concerns raised by IRB members and staff, a committee was established on an institutional level that monitored all projects seeking to enroll COVID-related populations. Also, institutional resources were used to mobilize established institutional banks as brokers for COVID-related data and biospecimens. This streamlined the process for collecting and distributing data and biospecimens related to COVID-19, which benefitted researchers and prevented the creation of countless standalone banks.

While this re ection has drawn attention to aws that presented themselves during the pandemic, I hope the quick institutional action and commitment of those in the HRPP are also apparent in the simple yet effective remedies described. Although the pandemic has presented numerous challenges to all involved in human subject research, it has also highlighted the research community's perseverance and dedication.

IRB Tales from the Heart of the Pandemic

Hallie Kassan

The week of March 9, 2020 started off like any other week in an IRB/HRPP of ce. Two new staff had started in our of ce within the past two weeks, and we were training them. There was talk of coronavirus and COVID-19 in the news as it had made its way to the US, but our health system was not yet feeling a major impact. Then, as each day passed, there were new developments. Rumors started flying that someone in the building in which the HRPP office is housed had come down with COVID-19. Staff started panicking. Leadership at work and within research reassured everyone that if we all follow the basic guidelines, we will stay safe. Those guidelines were wash your hands, cover your mouth when you sneeze and cough, and stay home if you feel sick.

By Thursday morning, March 12, 2020, it was clear that staff did not feel safe coming in to work any longer. The challenge that day was setting everyone up (including two new employees who had been with us for less than three weeks) to work remotely, as our work force was generally not remote. My assistant director and I worked with IT support to make sure everyone had a functional computer to use at home, with which they would be able to login to our network. By the end of the day Thursday, all the HRPP staff had been told they could work remotely until told otherwise.

Once the staff were settled, I was able to focus on work in the office and decisions that had to be made:

- Do we need to put out a notice closing down research? Or can we allow investigators to make their own choices regarding their studies and continued activity as long as it was in compliance with the health system policies being put forth to combat COVID?
- Will research studies be opening up? What IRB will be reviewing them? Our health system's IRB or an external IRB?
- For studies coming through the IRB, what type of turnaround are investigators expecting?

It became clear that research leadership had to put out a memo providing direction on how ongoing research studies should be handled. Investigators were confused and not sure whether they could move forward or not. They needed direction. Thus, over the course of a weekend, the HRPP worked together with clinical research operations.

Together, we sent out a notification requiring enrollment on open studies be halted. In addition, we asked for research activities to be paused, unless the studies were of potential benefit and pausing activity could cause harm to an enrolled subject.

The next agenda item was determining which COVID-19 research studies we should open within our health system. A small group was formed to vet all the COVID-19 trials that were coming our way and determine whether they were feasible to move forward. The decision makers felt very strongly that we should try to limit our trials to randomized controlled trials, in an effort to put the best science forward. The first trials we opened were industry sponsored multi center studies, for which we relied

on an external IRB. It was amazing how fast we were able to get these studies opened when all efforts across the organization were focused just on this. We opened up three trials within about a week of being approached about the studies. The health system's HRPP office worked side by side with the study team to assure all regulatory and institutional requirements were being met, as the study team was applying to the external IRB.

The industry trials opened and enrolled very quickly. The next focus was on an investigator initiated study that would be opened within our health system only. We are a 23 hospital system. Thus, even when we are a single site we have the opportunity to enroll participants at 23 hospitals. This investigator initiated study was the first COVID-19 treatment trial coming through our IRB. Fortunately, our IRB moved to a flexible roster video conference system in 2014. Therefore, the change to a remote environment did not impact the functioning of our IRB at all as our members were used to videoconferences.

We needed a rapid turnaround time for this review. The struggle was giving the IRB members enough time to perform an adequate review. We determined that our members needed the materials at least 48 hours before the meeting. We scheduled an ad hoc meeting based on when we planned to receive the study documents. Again, I worked closely with the study team to assure the materials came in on time. Remarkably, we had no trouble getting quorum for our meeting. I had been unsure whether our clinicians were going to be available for the IRB given the situation in the hospitals, but this turned out not to be an issue. The study went through one review and was deferred. It came back a few days later for another review. The IRB was able to approve the study within 10 days of receiving the original submission. The IRB put the study on a very short renewal period and asked for a continuing review application within 30 days of approval due to the rapidly changing information regarding COVID-19. The Committee wanted to keep close oversight of the study.

We continued to receive additional COVID-19 treatment studies for review. Rather than our typical 14 days from the day of receipt until the study is going on a meeting agenda, we put things on agendas as quickly as we could, generally within 2–3 days of receipt in our office. I sat on the committee that determined what studies moved forward, which allowed me to tie into the IRB and their agendas and save spaces for the studies which I knew would be submitted.

In addition to treatment studies, we had many researchers that wanted to look at the data from the COVID-19 patients for noninterventional studies. The health system put a committee together that reviewed the requests for these types of studies before the submissions came to the IRB, allowing an opportunity for refusal before IRB submission. This greatly cut down on the number of applications the IRB had to review. The HRPP Office set an expectation for investigators that we would review this type of research within two business days of receipt in our office. Being transparent on turnaround times helped to curb the constant barrage of questions such as "When will my study be reviewed . . ."

One of the biggest challenges in conducting the clinical trials was around consent. Obviously this was a unique situation that most had not dealt with before. Patients had to be in isolation and many were vented, so conducting the consent process was a challenge. In addition, due to the urgency of wanting to get patients on a study so we could learn something, and clinicians being swamped with treating patients, study teams had trouble finding people available to obtain consents. The organization's policy had generally been that a responsible practitioner licensed and credentialed to perform a procedure is the one that obtains consent. This is a organizational policy and not an FDA or Common Rule requirement. Thus, for these studies, the study teams asked that we allow folks that were not necessarily licensed and credentialed to obtain the consent—such as a study coordinator who is very knowledgeable on the study. After much discussion, the IRB worked out a process to waive our usual consent policy, as it seemed in the best interest of the participants to be consented by a person who has more time and can be thorough with the process. Study teams put together plans for training the consenters and procedures for getting participant questions answered if a question arose

that the person obtaining consent could not answer him or herself. The allowance of this process in this circumstance led to more successful trials while still protecting participants and providing an adequate consent process.

At the height of the pandemic in April 2020, our health system had 3400 patients hospitalized with COVID-19. As of September 2020, we had treated 85,000 patients across all of our facilities (outpatient, urgent care, in patient). This is 20% of all COVID-19 patients seen in the state of New York. As the pandemic starts to pick up across the country, and even now again in New York, here are the lessons I take away from our experience in the spring and will continue to use as we move forward:

1. Regulations need to be followed but you can look for the flexibility in them and guide investigators to conduct quality research while being flexible
2. Communication within research administration and to the study teams is essential. It is a fast moving environment and staying connected is important to assure efficiency of p ocesses.
3. Communication between research and clinical care teams is essential. This pandemic shone a light on research. All of sudden everything being done to treat patients was research. A coordinated effort between research and clinical teams can help maintain focus so that we can learn as much as possible from every patient treated during this pandemic.

Clinical Research During the COVID-19 Pandemic

Sujatha Sridhar

When the news about COVID-19 spreading in various parts of the world and then in New York City was reported the first week of March, it still seemed very distant. It was work as usual, but we started noticing institutions all over the country discussing ramp down plans as stay at home orders were being issued in various parts of the country.

The week of March 9th, the University started discussing ramping down plans for research. Laboratory-based researches were well versed with emergency preparedness procedures. After the devasting losses suffered during hurricane Allison in June 2001, laboratory researchers had developed a robust plan for preparedness, which they put to use several times since during hurricane season each year. However, there was not a similar plan for clinical research. Developing a ramp down plan for clinical research proved very challenging. Every research study is different—a plan for an oncology clinical trial with an investigational agent needed to be different from a research study on learning methods for elementary school kids. It was helpful for us to focus on the main considerations, which was to ensure the safety of participants enrolled in clinical research studies, minimize exposure of patients, participants and research staff and to be mindful of availability of resources such as PPE and other clinic and hospital resources. On March 19th, when Harris County and several other surrounding counties started instituting stay at home orders, we were ready with a plan. In addition to asking researchers not to enroll any new participants in clinical research that would involve in-person visits, the plan asked researchers to make case by case decisions based on these same principles for any participants who were already enrolled in clinical research studies.

IRB Operations

Our IRB has been using a fully electronic IRB system since 2004, so we were sure we could keep the IRB operations going during the remote working period. However, conducting IRB meetings virtually was not something we were familiar with. We were very proud of our high tech conference room with laptops, large screens and teleconferencing capabilities. Our only experience having remote participation was when we had a consultant or an alternate call in by telephone, or occasionally video conferencing. Our IRB members enjoyed the in-person camaraderie and we joked that each of our 4 IRB Panels had a character. We were not ready to meet virtually—so for the first week, we

had 8 people in the large conference room, socially distanced, with the rest of the members on WebEx. It was a disaster. Most of the time in the meeting was spent reminding members in the room to speak up because those on WebEx couldn't hear them. It was not dif cult to decide that our only option was to go a hundred percent virtual. It took a few meetings for us to learn how to conduct the meetings effectively and also practical matters such as recording votes of each member. Soon, IRB meetings were running smoothly with many members saying that they prefer this format and would like to continue to meet virtually even after the pandemic restrictions have eased. Most IRB meetings had record attendance and it was much easier to schedule investigators to join in to answer member questions. What had appeared to be an insurmountable challenge turned out to be an advantage.

In the first few weeks in this new era, we saw a slowing down of new submissions, mostly because no new enrollment was allowed in clinical research studies. Researchers must have felt there was no point in initiating new trials. However, this was just the calm before the storm. Within no time, there was a surge in research related to COVID-19. The number of new applications that our IRB received in 2020 was 25% higher than 2019. COVID-19 related research accounted for more than 20% of new applications to the IRB. Many of these COVID-19 proposals were urgent and the IRB office would receive calls and emails from Principal Investigators and research staff asking for an expeditious review.

In response to this urgency, IRB staff and members were asked to prioritize the review of COVID-19 protocols. IRB members also recognized the unique challenges researchers faced in conducting research during a pandemic. IRB members focused on ensuring that the rights and wellbeing of human subjects were not being compromised for the sake of expediency. For example, our IRB had advocated very strongly in the past for in-person informed consent discussions. However, in the light of this pandemic—while they agreed the necessity of remote consent process was necessary—they were diligent in working with researchers to develop a process that ensured that the remote process would be as robust as an in-person consent process.

In addition to the deluge of new COVID-19 related proposals, in the early months, the IRB staff had to also deal with several emergency use requests. For several weeks, IRB staff were on alert to deal with these requests all through the week, including weekends. We developed a system in which one staff member would be 'on call,' monitoring emails, and would activate a team of regulatory specialists, IRB staff, and IRB chairs to handle any emergency use requests. Often these requests meant we would have to drop everything else we were working on to ensure that all the regulatory paperwork to obtain the investigational agent were completed accurately and quickly. When we heard that the patient had received the agent, all the effort seemed worthwhile.

COVID-19 Research

Many of our frontline COVID-19 researchers and our clinical trials offices were receiving invitations to complete feasibility questionnaires for clinical trials for various COVID-19 treatments and diagnostics. Very quickly, we recognized that it would be important to have a process to identify trials that would be most beneficial to our patients and also trials that had the highest chances of successfully being done here in our institution. A COVID-19 clinical research workgroup was formed with a charge to select the most promising studies that could reasonably be implemented. The committee met twice a week every week to review all new COVID-19 related clinical trials. Only research approved by this group was allowed to proceed with IRB review. Reviewers scored protocols based on readiness, leadership, funding, supporting evidence, impact on field, and participant safet .

A COVID-19 subcommittee was formed to help integrate clinical trials into the already complex workflo . All researchers who were involved with COVID-19 clinical trials were invited to participate. This group met every other week by WebEx. This sub-committee developed a priority rotation schedule to ensure all trials have adequate opportunity for recruitment. Another workgroup was formed that consisted of research nurses and research coordinators who worked on COVID-19 clinical

trials. This group kept in close communication by sending daily emails with information on which patients are being screened and enrolled and which patients can be passed on to the next research team. We learnt pretty soon that it was important to communicate daily, and sometimes several times a day, to ensure that we were able to offer opportunities to participate in clinical trials to all our patients. It was also important for us to have current information on trial status—especially when trials were closed to enrollment by the sponsor, or when trials were being placed on enrollment holds by the sponsor for safety or other concerns so that other trials could recruit. We developed a dashboard, which was constantly updated so everyone working in this space had access to the most current information.

Conducting Clinical Trials During a Pandemic

While it was not too difficult to issue a rule to put a hold on new enrollment, it was a very challenging task to ensure there was a methodical and thoughtful resumption of new enrollment. Clinical trial investigators and research staff were invited to participate in regularly scheduled WebEx meetings to discuss concerns in conducting clinical trials during the pandemic and develop solutions. Our researchers and research staff helped us craft a plan for phased resumption of enrollment in clinical research. Researchers also shared tools they developed, such as standard operating procedures for home research visits to checklists for screening participants before study visits at the clinic. We were very thankful for the FDA guidance on conducting clinical trials during the pandemic and worked with research nurses and coordinators to develop guidance on remote study visits, remote monitoring, electronic consent, etc.

Lessons Learnt

The most important lesson we learnt was that communication is key. Looking back, perhaps we should have worked with clinical researchers and research staff before issuing the enrollment hold in the middle of March. Although it was necessary and important, having at least a preliminary plan for phased resumption of enrollment might have been more helpful. While we did put together a recurring meeting for clinical researchers to discuss issues related to conducting clinical trials during the pandemic, we should have initiated these meetings much earlier in the process, even before the enrollment hold's announcement.

We quickly realized that sending multiple emails to our research community created confusion instead of clarity. Instead, we developed an intranet site and a Google Drive folder to share information with our research community. This site was continually updated as we received new information from regulators, or as we learnt from our fellow institutions around the country.

We also learnt that it was not easy for the Covid-19 committee to disapprove proposals. Our default mode was to work with investigators to improve the protocol. However, with numerous competing trials for the same patients, it was necessary to develop a rubric by which we could deny protocols that did not meet the committee's standards had set. Again, focusing on the first principles, which were ensuring access to the highest quality trials for our patients and only accepting trials that had a chance of successfully being implemented at our institution, helped with these decisions.

Communicating often and clearly with everyone is key. Ensuring we seek and listen to voices from as many groups of people as possible is very important. Being transparent about the process was helpful in gaining the trust of the research community as we all navigate these challenging times together and learn together.

Planning an Agile Response

John D Tupin

Our IRB reviewed just over 200 COVID-related studies with an additional 170 individual actions in relation to those studies.

Social behavioral ranged from studies addressing PTSD among front line workers to transitions to telemedicine care; many of our studies focused on underserved and racially diverse communities. Biomedical and clinical studies addressed early efforts to evaluate the efficacy of remdesivir, convalescent plasma, and vaccines. Imaging studies included detection of ancillary effects on organ systems and inflammation. The university also created and validated high throughput, up to 56,000 tests a week, saliva-based testing.

One of the challenges we faced was emergency use. Our first encounter with COVID-19 occurred in early 2020. The subject was in critical condition, incapacitated and on a ventilator. The patient had no definitive COVID diagnosis as the test was withheld by the responsible public health agency owing to irregularities in symptoms. However, due to the nature of the virus we made the decision to move forward with the manufacturer to treat the patient in the belief that the formal diagnosis would be made and coincide with administration. The IRB made the decision to verbally remote consent the legally authorized representative (LAR), with a waiver of documentation until the immediate hazard could be eliminated and document the process concurrently with written consent at a later time.

Our early experience in obtaining treatment medication was rocky. The original study was funded by NIH and as such was beholden to a single reviewing IRB. At that time I believe that the potential scope and impact was less understood. As such, the reviewing IRB had not considered "out of network" providers and researchers and had to delay until institutional approval could be obtained. The problematic issue here was the unavailability of the institutional decision maker and no process for emergency delegation. I can't blame them, as this was new territory. It was apparent to the IRB and the potential PI that it was necessary to add a second IRB of record. The sponsoring agency was contacted and apprised of the issues; shortly thereafter a second IRB was activated. The additional IRB was structured for multisite studies and had a great deal of experience in pharmaceutical studies. Further, the second IRB employed Smart IRB, allowing for a streamlined reliance process and quick activation. Moving forward, we have developed a robust delegation chain and will advocate strongly for an expedited waiver of the single IRB requirement.

The university has been an active and leading center for telemedicine, however, COVID 19 produced some interesting issues. First, there were many commercial services that provided peer to peer programs that are easy to use and accessible to the majority in the community. That meant that providers and researchers were no longer tied to proprietary, homegrown systems that required specialized hardware, software and user accounts generated by in-house IT. However, it presented a new host of issues. Security concerns including data transmission, encryption, storage and ownership became a very important issue. Best case scenario data was being transmitted only and never backed up or duplicated. But what if it was? And where were the duplicates residing: dedicated domestic servers, in the cloud? Were the systems HIPAA or part 11 compliant?

Additionally, what about rural patients, the homeless and impoverished, or my 86 year-old father who uses his laptop as a paperweight? We quickly were able to identify systems and vendors that we had used in patient care as secure and validated a handful of others that could be used during the public health crisis. What remains to be done is a clearer way for new vendors or those who did not intend for their systems to be used in medical treatment to validate their products in a way that is acceptable to the end user and the vendor. As to the underserved communities, how to make the technology available in a safe secure way that addresses all of the above issues and public safety needs to be studied and addressed.

Another challenge we faced, and one of the now-obvious issues that we didn't consider, is the budget crunch that has been created at academic facilities. The university where I work is situated in a college town. Without our students, our population drops by as much as 35,000. This has impacted not only the community but the campus. At this point our office of research has enacted a curtailment plan that has resulted in a two week closure with only

emergency support available. We are covering and meeting our standards, but we are unable to address new non-urgent submissions.

As to the advice we have for other IRBs that review research on pandemic illness: we lived by the belief that subject and staff safety always came first. To that end, we made adjustments on the fly to reduce or eliminate contact, community travel and non-essential staff presence at our facilities. The good news is it seemed that we were slightly ahead of adjustments being made by regulatory agencies, subject communications and form of documentation, but I worry that some of the actions we took will result in a disqualification of collected data. My team will be creating a large-scale event management plan based on highly a contagious viral threat that will allow our team to continue to be highly agile and effective.

Another piece of advice for IRBs: be prepared! Have an effective HIPAA and part 11 compliant system for moving data. We have had 15% staff take extended time off and one abruptly resign. Allow your staff to flex their hours and take mental health days, know that you will lose members of your staff due to stress, family care and illness and accept it. This isn't normal and trying to maintain normalcy is a fool's errand, but if you put a priority on staff wellbeing, there is a possibility that you will end with an intact team.

Researchers who study a pandemic illness should begin to advocate now for policies, technologies and emergency plans for the next pandemic. Without researchers' pushing there is a possibility of returning to our old normal.

Shaken

Ann Johnson

In response to the COVID-19 pandemic, work-at-home mandates for the university where I work in Utah began on Monday, March 16, 2020. The University's IRB approached the work-at-home situation with a can-do attitude. We weren't sure exactly how this pandemic was going to take shape, but we were going to make it work. We started marking things off of our checklist with semi-confidence

- We figured out our virtual conferencing platform.
- We wrote some initial rules of conduct for the convened meetings and disseminated them to our members.
- We bought everyone a new set of headphones with a microphone in hopes we would have sufficient sound qualit .
- We trained two of our staff members to be meeting hosts (affectionately referred to as 'meeting Yodas'), to guide everyone to virtual meeting bliss while trouble shooting all technical problems and helping IRB discussions to go off without a hitch.

On Monday, March 16, we felt good. We had taken on the initial pandemic stress and subdued it into submission. We were ready for our first virtual convened IRB meeting at noon on Wednesday.

Then Salt Lake City experienced a 5.7 magnitude earthquake at 7:09 AM on Wednesday, March 18.

The thing that stood out most to me about the earthquake was how loud it was. Many of us in Salt Lake City were still in our beds at 7:09 AM and we were not only shaken awake, but startled from sleep by the rumbles and groans of our houses. My house rattled and boomed around me as I clung to my newborn baby and my husband ran for our toddler. The IRB staff spent the morning checking in with one another, feeling out our emotions and reporting on the state of our foundations, our pets, our WiFi. Luckily the whole of Salt Lake City experienced very little damage and the population was safe; no injuries or fatalities. We hadn't been devastated, only shaken. We decided everything was okay enough to go forward with our virtual-convened IRB meeting scheduled at noon. We experienced more than four dozen aftershocks that day. The largest—a 4.6 magnitude quake—occurred at 1:12 PM, smackdab in the middle of the convened IRB meeting. The IRB chair paused in his review, while everyone watched each other shake in their

video squares on the screen. We continued to feel aftershocks for a few weeks, and each one would trigger that rudimentary fear for one's safety, the fear of the unknown, and the fear of losing control.

The day of the earthquake brought a dark cloud over the IRB staff's personal confidence for mitigating the cumulating stress. Our mood toward the pandemic's onset turned from inquisitive to somber. Though the pandemic and the earthquake were not correlated in any way, a new level of seriousness washed over us as we grappled to understand how to re-exert any modicum of control over our changing lives. We yearned for normalcy in a way distinct from the rest of the world who was also being upended by COVID-19.

Many of us at the IRB found there was one thing we *could* control: the review of research. Projects to study the various aspects of SARS-CoV-2 infections, testing, treatments, and pandemic social conditions came pouring in, with 32 pandemic-related projects reviewed and approved by the IRB within the first 30 days of the work-at-home mandate. We threw ourselves into the fervor for getting these studies reviewed and approved quickly, feeling it was our way of contributing to the pandemic's eventual end. We were able to prioritize these studies and complete our reviews in a fraction of the time were they to have entered our normal review queue (although, it required that non-COVID-19 studies be pushed back in the review queue). We convened some urgent IRB meetings that were not part of our regular schedule; because we had a panel with a quorum of three, we were able to quickly and easily find three IRB members at a time (out of over 100) who were willing to do urgent reviews and convene off-schedule. Having this panel already established pre-pandemic was one of the keys to our success.

We also took a flex ble approach to using a single IRB process for multisite research. In cases when deferring to an external IRB would save time and resources, we did so, recognizing the value of previously established reliance relationships that we could benefit from easily. We also noted cases where using a single IRB process would actually create greater time delays and burden for the study team, and thus opted to perform the reviews locally. This flexible approach ended up being something notable to the federal Office of Human Research Protections as well, as they granted an exception to the requirement to use a single IRB for cooperative research initiated during the pandemic "where reliance on a single IRB would not be practical".

Lastly, we solidified guidance for conducting remote consent processes and assisted investigators one-on-one to create situationally appropriate consent processes that met the conditions of the regulations. Except for a few pandemic-induced consent process exceptions for clinical trials granted by the Food and Drug Administration, all of the consent processes we approved fit within the existing regulatory framework. We, as well as investigators, were reminded of the many options for obtaining informed consent that already existed and have noted that their use should continue post-pandemic to the benefit of our varied participant communication needs.

Overall, our IRB's success came down to pre-existing options for flexible review and conduct of research. While we had not planned for these options to be specifically useful in a pandemic situation, they ended up being instrumental in reducing the number of barriers a COVID-19 project would experience. The flexibility created agility, which reduced our stress and restored our morale. The IRB was an effective partner in COVID-19 research, doing our part to benefit the wellbeing of our community and lay a foundation for future normalcy.

Late in the evening on Friday, March 20, I received an email from a physician after the IRB had approved his protocol at an off-schedule meeting that afternoon. After a tumultuous first week of pandemic life, it was a message that soothed me and has stayed with me for the rest of the year. It continues to put the pandemic—and the IRB's work in it—in perspective, despite an earthquake or any other emotionally destructive force.

> "Forty-eight hours ago, we had an idea about how we might help these COVID patients. Since that time, we created a team, drafted a protocol, and filed an IRB application that was expeditiously reviewed. I'm not one for the heavy emotional thing, but the speed and cumulative

institutional effort to make this happen was inspiring. Whether or not this is a viable therapy remains to be seen; our commitment to patients, however, remains truly exceptional."

Emergency Response to COVID: An IRB Story

Joan B. Cobb Pettit

In past "normal" times, when IRB members and leaders think about "emergency response," we imagine hospital emergency departments or public health mobilization efforts in the face of an epidemic or other health crisis—with the focus on helping others. COVID introduced a new perspective because the emergency we faced affected us personally and professionally, in addition to our researchers and our study participants. It forced changing so many facets of our work: halting in-person human subjects research activities to reduce risk, moving IRB operations to remote work, minimizing unnecessary submissions when studies shifted from in-person to remote work, providing guidance on how to safely collect data using remote mechanisms, and working with University leadership on how to safely re-start human subjects research. And it was all so sudden—or at least it seemed that way.

At the Johns Hopkins Bloomberg School of Public Health (JHSPH), we have an office of 10 people and two IRBs that meet weekly. We process about 500–600 new applications per year, including Exempt, Non-Exempt, and "not human subjects research" submissions. Our portfolio includes research all over the world. In late February, 2020, our Vice Dean for Research, who oversees the IRB Office and all research activities at the School, was involved in discussions with JHU leadership anticipating that the University would need to move to remote work. He asked me to come up with a plan for the IRB Office. I worked with my staff of 9 and on Monday, March 2, I sent him an email outlining what we came up with:

1. Communications: Change our telephone voice messages to tell folks to communicate via email. Inform the IRB Chairs and Members about our plan and help them access Zoom if needed.
2. Computers: Make sure all staff have computer access at home—and let them take office computers if needed.
3. Internet access/fi ewall: Have staff test access to office databases and systems from home and obtain IT assistance if necessary.
4. Office files: Create electronic files for any hard copy files that we maintain in the offic
5. Zoom: Set up Zoom accounts to permit our weekly IRB meetings to proceed electronically. Learn about Zoom—who needs to have accounts, how to host meetings, send new meeting invites for all standard meetings with Zoom link.

And finall ,

6. Set up a test day for staff to work from home to make sure everything worked.

We chose Monday, March 16, as our test day and spent the rest of the week having staff check out and resolve internet access issues from home, scheduling Zoom meetings with each other, and trying to work out the kinks in our plan. By the time we had thought through all the logistics of transporting computers back and forth, we decided that it would be better to have us schedule a test week instead of a single day. So the plan was to work from home the week of March 16.

But then, life and COVID intervened. The virus was spreading and a shutdown loomed. By Wednesday, March 11, the School and University began communicating the possibility of having everyone go home and initiate remote work. Thank goodness we had a plan and everyone knew what to do.

My personal story has a little twist. We have a son and daughter-in-law living in Wellington, New Zealand. They were expecting their first child in late March, with no other family nearby. We planned to visit in April. On Wednesday, March 11, they called us and said that the New Zealand government was calling all Kiwis home in anticipation of a border closing. The message was, "Come now or you won't

be able to come later." We scrambled and moved our tickets up to Saturday, March 14. I informed the Vice Dean of my situation, and I remember him saying, "If you go, what happens if you can't come back?" I sort of shrugged my shoulders and said, "We'll see what happens."

Our granddaughter was born on March 14 (NZ time), while my husband and I were packing that Friday night. We flew on Saturday and arrived Monday morning (NZ time), the first day of mandated 2 week social isolation for travelers. The border closed on Thursday, March 19. So began my "very remote" working.

Back in Baltimore, our staff initiated their work from home plan, and it went smoothly. We had a few kinks but were able to resolve them fairly quickly. Fortunately, we had no staff absences or losses since the COVID period began. Meanwhile, the University shut down all in-person human subjects research, except for COVID-related research and some oncology studies. Leadership worked long hours on developing plans for various aspects of the University enterprise, with research as one element, including: establishing guiding principles for the gradual resumption of in-person research; ensuring the health and safety of faculty, staff and students; addressing re-opening of lab research and human subjects research; and deciding how to manage undergraduate research. The plans for the different divisions needed to be based on an understanding of their most urgent concerns and coordinated as a University-wide COVID Response Plan. My first weeks in social isolation involved daily phone calls with the JHU Vice Provost for Research, the General Counsel's Office, the JHU Chief Risk Office , and the IRB Directors and Institutional Officials from the 3 IRBs at JHU: School of Medicine (and Johns Hopkins Hospital), Public Health, and Homewood (liberal arts and engineering). These calls were so important, as they allowed us to discuss the quickly evolving, and quite scary, situation in real time. After the first 2 weeks, we went to 3 meetings per week, then 2 per week, and then stopped until we needed to update the Phase procedures in October.

We ultimately established a Tier system to categorize ongoing studies based on direct personal benefit to participants, with a Phase system to match the institution/local conditions with the risks of in-person contact. We decided to encourage investigators to move all in-person research data collection procedures that could be performed virtually to remote. Telemedicine efforts increased exponentially on the clinical side, and researchers followed. Interviews and focus group discussions moved to virtual platforms.

The challenge was how to implement these changes in a compliant way without overloading the IRB and the IRB member-reviewers, and avoid confusing investigators by communicating clearly to faculty, staff, and students. We kept the IRB review of research protocols separate and independent of other COVID-response safety reviews. As a result, the IRB's review considerations have not changed except for assessing new vulnerabilities for populations particularly at risk for COVID. We made the following decisions for Phase 1:

1. We decided that changing in-person research from in-person to remote constituted a change driven by an emergency situation, and that investigators who made such changes to reduce risk to participants did not need to submit an Amendment to the IRB until after the Emergency period ended.
2. Only Tier 1 in-person research activities (direct personal benefit) and COVID-related studies could proceed, but there needed to be some new non-IRB safety review of those studies to make sure COVID risks were minimized.
3. The University established guidelines for symptom screening, PPE requirements, social distancing, and cleaning protocols. We needed a new process for reviewing all in-person studies to ensure that they met these new guidelines. Each JHU division created its own process. The School of Public Health created the Human Subjects Research Restart Committee (HSRRC); the School of Medicine delegated safety reviews to medical departments and created a Prioritization Review Committee to consider resources needed for clinical care with the increase in patient volume. The SOM was concerned that research activities would compete for resources (for PPE, personnel for services like imaging, space in clinical settings complicated by social distancing, etc.) The School of Medicine's IRB did not take on

management of their restart committees; the JHSPH IRB office did

4. We needed a website to explain all the new requirements and provide a form through which investigators could describe their Safe HSR Protocol Plan. The form captures information about: 1) study location and the role of the JHSPH investigators and collaborators; 2) the safety plan for study staff (screening, PPE, transport, cleaning protocols, contingency plan for meaningful exposures); 3) a similar safety plan for study participants; and 4) the safety plan for the site (location, site plans, density and traffic flow of people coming through the site, duration of staff-participant interaction, cleaning protocols).

We asked several faculty members to join the HSRRC, some of whom also serve on our IRBs. We included investigators doing clinical work in Baltimore, and researchers who work internationally. We quickly found that while JHU leadership wanted consistent standards and requirements across the globe, and that meant imposing the very strict protocols and PPE requirements needed in Baltimore, standards in international settings involved other considerations. For example, no in-person focus group discussions (no direct personal benefit and prolonged in-person interaction indoors) were permitted in Baltimore in Phase 1. But in many international settings, COVID conditions were better. Having a focus group meet outdoors (10 or fewer people, all masked and socially distant) could be justified. We established a different standard for international studies that would permit focus group discussions. A second example involves the use of face shields for in person interactions; face shields are standard PPE in the U.S., but for household visits with non-clinical data collection in developing countries, they could cause fear or distress. We decided to ask each investigator to tell the HSRRC about the current guidelines in country so that they could consider deferring to local standards.

Once the "emergency" period ended in June/July, and it was clear that we would be working with COVID for a while, we needed to ask investigators to submit Amendments to the IRB to make sure that whatever data collection mechanism they would use going forward was documented as approved. If investigators wanted to continue with in-person interactions with study participants, they needed to submit their Safe HSR Protocol Plan for review. If they were going to keep their procedures remote, they needed to Amend their protocols to explain how they would collect the data using best data security practices.

It's been a challenge coordinating IRB reviews with the HSRRC reviews, as we are using the same electronic submission platform for both efforts. In the beginning, the HSRRC submission came in as a separate "Other Submission" and involved ongoing studies that wanted to restart data collection after a COVID hiatus. The review was separate and distinct from the IRB review, but sometimes required changes to the study protocol document—so we had to track those studies to make sure the investigator actually submitted the Amendment. Now, the HSRRC agenda consists mostly of new studies, so we've made HSRRC approval part of the initial review of the research application.

Our IRB staff has been amazingly dedicated and resilient in the face of personal challenges, like having to home-school children or monitor parents in nursing homes. We are so fortunate because we have a very stable staff of senior analysts and coordinators. Our IRB members are working so hard and are on Zoom calls all day with teaching and administrative leadership obligations. Single staff members and older staff and IRB members have been alone for months. We have maintained our weekly staff meetings to document our SOPs as they change, to discuss new developments, and to keep our connection strong.

What worked for us?

- Anticipating going remote and working through a plan in advance of needing it
- Communicating with our researchers, IRB members, and leadership about adapting to working with COVID in our lives
- Being flexible in applying the HSR regulations during the emergent period
- Ensuring that after the "emergent period," researchers updated their research plans to reflect cur ent data collection methodologies
- Meeting weekly with IRB staff to resolve operational issues and keep in touch.

In December, 2020, I'm still in New Zealand. We have not yet focused on what the future of IRB operations will look like. Our IRB Chairs miss the dynamic of in-person IRB meetings; our staff really like not having to commute and dress for the office I've been very impressed by how dedicated our IRB members and IRB staff have been through this period and am gratified that I have the privilege of working with these wonderful people.

Pandemics and Protections: How to Keep It All Together in 2020

Gabrielle Rebillard

It is not unusual for even the most experienced, well-resourced IRBs and HRPPs to be in survival mode. The churn of requests for priority review, funding and academic deadlines and requests for help with applications never cease. The staff must juggle their own workloads and perfect their craft without sacrificing customer service. Meanwhile the QA/QI initiatives never seem to be finished and other areas of research operations need your assistance, too. The old adage "if want something done, ask a busy person" seems to be standard operating procedures for IRBs and HRPs.

The topic at hand is what happens when more chaos and challenges are thrown into the mix of an already difficult job. Collectively we may avoid even questioning whether 2020 could get much worse for fear of knowing the answer is "Yes." We are left to wonder if our IRBs and HRPPs will become victims or champions of circumstances. Maybe human research protections seem relatively insignificant when the world is so upside down? The truth is that we, members of the very entities responsible for protecting the safety and wellbeing of others, are ourselves human. This pandemic has changed the "where" and the "how" but not changed the essential nature of "what" we do. We are still the "go-to" compliance experts for researchers trying to keep old projects going and launching new ones. We remain key partners in the machine of research operations. Now we just meet our responsibilities and deadlines in makeshift home offices. We try to focus on difficult reviews while competing for internet connectivity, tuning out family activity, and caring for our own mental and physical health. COVID has created real and existential risks to our personal lives while all the same compliance standards remain in place.

While dealing with COVID-19 more than enough on its own, the fact is that it is just one of many serious challenges our institution has faced in the last year. Prior to the March lockdown, our university and its academic medical centers was already in turmoil. We were (and still are) dealing with the closure of one hospital system and establishment of new partnership for another while simultaneously also undergoing the process for our AAHRPP re-accreditation. Did I mention that we are also replacing our electronic research software system? So, adding chaos and challenges is not hypothetic. It is our "norm."

How are we getting our compliance work done? Let's start with the basics. The closure of our university was somewhat anti-climactic because of previous flood damage to the HRPP's building. (Yet another fun part of this year). Staff was already moving towards remote work or finding temporary workspaces in the building. We were already running business operations online as much as possible. What stopped were the impromptu door-way conversations and the in- person training sessions for researchers and students. Without a commute, some staff started earlier, and some started later or work intermittently to accommodate a revised home-work life balance. The monthly meeting for our three IRB Committees went virtual.

On the whole the type and balance of the research we review has not shifted radically because of the pandemic. Instead a new focus emerged. Initially we began seeing clinicians scrambling to submit Emergency Use and Expanded Access applications. I got an early Saturday morning call from a Dean about a hot opportunity for collaboration which lead to a weekend's worth of conference

calls, regulatory debates, and review work to meet a Monday morning deadline.

I have to confess that prior to March 2020, I did not expect to ever be in situation or see a project where I needed to dig into this part of the Revised Rule:

"(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters)."

But in the early stages of the pandemic, it happened. A project came into the office that had a very tight deadline and with a debate already going. The funding source felt that a project should meet Exempt Category 5 but another collaborating entity (a Federal agency) argued that it meets criteria outlined in the Revise Rule as not being human research. I stood in the middle listening to the debate. I quickly went to the "regs" and then the OHRP website. I picked through the de nitions, the current discussion, the facts of the protocol and the points made by all the involved parties. As the Director of the HRPP, my job was to help translate the Revised Rule to clinicians and people in the research operations. All wordsmithing and arguments aside, what broke the debate was me pointing out that we were deciding between something that fit a specific category as not human research and something that was determined to be Exempt from IRB oversight.

Ultimately, I pushed our researchers to go the conservative route and to require submission. I felt it was better to "err" on the cautious side, which I hesitate to say is "erring" when human subjects are involved. The IRB conducted its limited review and the final determination was Exempt 5. Decisiveness hastened the review and does not denote a lack of diligence. We had the correct discussions about the nature of the research and the nature of what seems to be a very gray area of the Common Rule. In the end, we ended up being the firs IRB amongst all the collaborating institutions to get its review finished. Being first should not be confused with being the best. In this case it helped with institutional prominence for the researchers involved.

Aside from clinical research and trials, COVID-19 has also increased research across and among Social / Behavioral fields. Investigations with varying focus from effects of quarantine on mental health, the use of parks during a pandemic, and epidemiology in the context or race and economic class.

I have found myself in warp drive to help process something I had no experience with: an Expanded Access Trial (one of 25 sites in the country) including a reliance agreement. Since this is 2020, this happened to coincide with the formalization of a new business partnership with one of the hospital systems. (Same hospital. New owners. Unclear org chart or operating practices). It is amazing how fast things can get done when the pressure is on. What never changes is how hard it is to find balance. Not all pandemic research is under tight timelines and not every project has to be reviewed yesterday.

I have proudly watched our IRB Committees (particularly those dedicated to biomedical research) consider the current political landscape as it shakes the federal entities (the NIH, the FDA, the HHS etc.) with whom we interact. There is a type of renewed commitment to honor the spirit of our institutional policies and standards. We can adapt but we do not have to compromise. We can push for answers and extra support even when the promise of academic or financial gain are rightfully at our proverbial door. In other words, we have become a better IRB because of the pandemic. This is exactly what crisis is supposed to do if it is to be transformative rather than purely destructive.

Generally, there has been a mad scramble to submit Modifications (and to a lesser degree Reportable New Information). Some researchers want to let us know that they were halting enrollment and research activities. Others want us to know that they were changing how the research was being conducted during lockdown, like including remote

procedures. Some wanted to insert language from the CDC about the masks, physical distancing, and handwashing. I got pulled into countless meetings about closing the University on a temporary and then semi-permanent basis. This morphed into committees and sub-committees about "ramping down" and "ramping up" research. We track phases of shutdowns and reopening at the local, state, and federal level. We look sideways to other universities for guidance. I call up other IRB and HRP colleagues for practical advice and perhaps a laugh or a virtual hug.

I did craft some guidance language to put on our webpage. It had to be general enough to be applicable to the wide audience of researchers we serve yet be specific enough to be useable. It had to consider the capacity of the IRB staff and compliance standards for the research. I have to temper my reviews of new information knowing full well that people were following my advice to take immediate measures to mitigate risk to subjects and others (including the research staff themselves) and tell us when they could proactively make modifications when possible, or as part of a follow up to the RNI.

Lest this discussion continue to drift into the weeds of research compliance, I want to get back to the IRB staff and the extended members of the HRPP. Clearly, the pandemic effects working conditions beyond just telecommuting. It is personal. It makes people sick and live in fear of becoming sick. It has meant that the merit-based bonuses, cost-of living increases and contributions to our retirement funds have all gone away. It has meant layoffs, hiring freezes, and other cutbacks. It means trying to find some quiet you can work in when you live with others, and it means fighting loneliness and isolation for folks living alone.

How does someone in leadership keep the compliance machine moving in pace with the flow of new and continuing research AND keep up with the needs of the dedicated staff. For me it has come down to flexibility and vigilance. The ethical and scientific principles that we apply to research are not lost on those of us who review the research. That consideration for risk/benefit goes for us too. We cannot ask for people to suspend or ignore the concerns of the world and their immediate lives when they do their reviews. The opposite has possibly never been truer. COVID-19 and its impact on everyone (researcher, non-researcher, participant, or reviewer) is a type of reckoning. We need flexibilit when we ask our team members to do high-quality, efficient reviews and to take care of the endless administrative details when they are homeschooling kids. Encouraging people to take physical and mental health breaks is every bit as important as any of my other responsibilities. I also have to remind myself to do the same because, when your desk is at the foot of your bed, you literally start and end your day with your computer staring at you.

The "vigilance" part is channeling our energy into the same thing we have always done: keeping the safety and well-being of our participants as the reason for our work. We do this remotely with the help of SharePoint, Zoom and an eRA. The operational structure is less formal but surprisingly/happily no less efficient. We still have the CFR. We still have AAHRPP standards. We have a research community counting on us to help them remain in compliance and a team of operational partners hoping we will do the same for them. After all that is said in done, a pandemic just shows us what we already knew: IRBs and HRPs are champions regardless of their circumstances, human research protections have never been more relevant, and none of this happens without exceptional people working on these teams.

COVID-19 Story From an IRB Member and Administrator

T. Howard Stone

Introduction

Declaration of the COVID-19 national emergency has had and continues to have a profound effect upon what human research studies are permitted, how permitted studies are conducted, review of these studies, and the guidance that is provided to the research community

at the university where I am an IRB member and administrator. From the almost instantaneous cessation in all human research activities to more recent discussions about phasing in permitted human research, human subject safety and well-being has been the touchstone. Ensuring that every corner of the University's research enterprise is provided current, relevant, accurate and useful information and resources about COVID-19 and human research, is a priority but resource intensive in the review and oversight of human research. Until the COVID-19 emergency is lifted however, COVID-19-related limitations on human research will remain in effect.

Cessation of Human Research

Prior to and very soon after the March 13, 2020 issuance of the Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, University leadership issued a series of announcements about imposing a wide range of scaled-up steps to prevent the spread of COVID-19, including new disinfection procedures, quarantine and isolation requirements, remote teaching, cancellation of events and activities, and remote work. These steps were often tailored to the context and environment in which human activities and interaction took place, including, for example, local, national, or international locations; office, classroom, laboratory, off-campus or clinics; teaching, service or research settings; and student, staff, faculty and visitor populations. Considering the precautions that were imposed, the Vice President for Research, Office of Research, and I discussed the implications of the national emergency and University actions upon research involving human subjects. The discussion centered on plans for the University's research leadership to announce a halt to all on-going and planned human research with reference to some possible, limited exceptions to be later explained. The halt impacted OHSP and IRB's operations and reviews, staff and member safety, initial and on-going messaging, and other avenues of communications that the OHSP and IRB provide to the research community. Thereafter, on March 23, research leadership announced as a policy matter, the cessation of research activities that involve in-person interactions or interventions with human research participants ("cessation"). The announcement provided general information about the cessation, specific exceptions, links to additional information and contacts for further questions or concerns. The objective of the cessation was to immediately stop any in-person face-to-face human research activities except for COVID-19 research that involved substantial likelihood of direct and meaningful biomedical or behavioral health-related benefit or outcome. Certain clinical trial activities taking place in licensed health care facilities or offices within the context of a necessary clinical care visit for which activities could not be performed remotely were also allowed to continue. Particulars of the cessation were subsequently provided to the state university system's Board of Governors for their own deliberation of COVID-19-related precautions.

Early Actions

To help ensure the broadest possible dissemination to the University community of the cessation policy, the announcement of the policy was published on the main public-facing web pages of the University, Office of Research and Office for Human Subjects Protection (OHSP)/IRB. The University and Office of Research pages included links to the OHSP/IRB home page. Additional information and links to a special COVID-19 and Human Research Studies page were provided. Prominently arranged on this special page is first stated the underlying policy for the cessation and their links. The list of research activity exceptions and their criteria (e.g., no persons deemed at higher risk for severe illness from COVID-19, including persons aged 65 or more years may be included at subjects in any in-person research activity) followed. Requirements for excepted studies (e.g., remote activities where possible; COVID-19 screening; maximizing social distancing; use of protective equipment such as masks) were next. Then, specific instructions for halting non-excepted study activities, such as notices to enrolled study subjects and minimizing

risks to subjects for whom halting study activities may be harmful; submitting for IRB review modifications of study activities to remote or virtual interactions; and links to new standard operating procedures, templates (including for COVID-19 screening and consent), and other OHSP resources (e.g., worksheets, a COVID-19 human research decision algorithm, FAQs and other COVID-19-related guidance). IRB members were informed of the requirements and the information and resources provided to the research community.

Additionally, a March 31 COVID Town Hall hosted by OHSP/IRB for the University's human research community was widely publicized, held via Zoom, with an audio recording and the slide deck of the Town Hall also published on the OHSP/IRB COVID-19 and Human Research Studies web page. To sustain dissemination and discussion of COVID-19-related information relevant to research generally, through Mid-September the Office of the Vice President for Research hosted widely publicized virtual weekly meetings for the University community. At these Zoom-based meetings, current and developing information about federal, state, and campus initiatives, funding and policies were shared. Researchers could pose comments and questions and participate in Zoom chat functions. Links to resources and points-of-contact to obtain additional information were provided. As OHSP Director, I participated in each of these COVID Town Hall meetings to provide human research-related information, be available for human research-related questions and concerns, and to take back suggestions, requests or ideas about how the OHSP/IRB might improve upon our COVID-19-related human research resources. A frequent and common outcome of these Town Hall meetings were the expressions of research community participants' appreciation about these meetings and their value.

Accompanying these early actions was of course ensuring continuity of human subjects review operations, certainly as a matter of regulatory compliance and as a measure of allowing important human research to safely continue. In the summer of 2019, all human research protocols were submitted and reviewed using an off-the-shelf electronic protocol management system (EPMS), allowing for paperless handling, documentation, record-keeping, and archiving of human research studies. The EPMS, as well as the routine use of other electronic and telephonic communications with the human research community, meant that very few researchers visited the OHSP/IRB physical offices, which incidentally were located nearby but off the main University campus. The availability of a wide range of information, instructions, and other human research review resources also allowed people to find what they needed without having to visit the physical office. When remote work was imposed for the OHSP/IRB, any disruption to workflow or communications with the University human research community was minimal. Desk telephones were forwarded. Email signature blocks included emphasis on electronic communications and use of EPMS for any study-related concerns or questions. Physical visits to OHSP/IRB became internet- or telephone-based. IRB meetings, discussion, and voting, were hosted on Zoom and agenda items and related review documentation and decisions were posted to the EPMS. Notices about remote review and operations were posted on the OHSP/IRB web page and outside of the physical office doors. OHSP/IRB members and staff, as well as the human research community, expressed satisfaction with remote staffing and eview of studies.

Review Processes

Considering the urgency of mitigating COVID-related risks to human subjects, the OHSP/IRB prioritized its review of human research. This prioritizing was conveyed to the University research community through the Town Halls and web pages, related online materials, IRB meeting announcements and emails, OHSP staff meetings, and as needed through ad hoc communications with individual researchers. The imperative of protecting human subjects' health and welfare compel that review precedence be given to any report of COVID-19-related issues or unanticipated problems. This includes subjects or study staff that test

COVID-19 positive or have been exposed to persons with COVID-19. These reports are handled in an expedited or convened review pathway depending upon the circumstances and need for changes to study procedures. The OHSP/IRB FAQs were developed specifically to ensure that study teams, OHSP staff, and the IRB know how to respond to such issues or problems. Non-COVID-19 incidents that implicated human subjects' health and welfare received similar precedence.

Next in review priority are modifications to currently approved or exempt research when these modifications involve transitioning in-person to remote or virtual activities. Using early available OHSP/IRB instructions and templates, these modifications are readily processed with few hiccups. After these modifications, precedence is given to submissions for COVID-19 research, either as new studies or modifications to currently approved or exempt research. The potential to explore or advance COVID-19 knowledge was considered inherently important given the paucity of such knowledge, enough to be prioritized above other non-COVID research. There have been many more modifications to transition to remote or virtual activities than new COVID-19 research activities. Finally, once any prioritized research is processed and scheduled for review, other studies or activities not included above are placed in the review queue. That could include modifications to currently approved or exempt studies and new studies, including other studies that are excepted from COVID-19 requirements (e.g., certain clinical trials only taking place in licensed health facilities or studies with a substantial likelihood of direct and meaningful biomedical or behavioral health-related benefit or outcome)

Some new procedures have been added to the human research review process. First, all study submissions undergo an augmented pre-IRB review to determine that COVID-19-related requirements are satisfied (e.g., remote or virtual in lieu of in-person activities, involvement of persons not considered at higher risk for severe illness from COVID-19, and COVID-19 precautions for excepted in-person research activities, including social distancing, use of protective equipment and sanitizing.) Use of OHSP/IRB provided instructions and templates (including a COVID-19 information sheet to provide to study subjects) help to ensure that study staff are aware of and implement these requirements. If not, these instructions and templates provide the OHSP/IRB with ready references to which study staff are pointed. OHSP staff communicate their pre-IRB review findings to IRB members assigned as primary or expedited reviewers. IRB members provide another layer of ethical and regulatory review that will also consider COVID-19-related precautions and considerations.

Second, an ancillary review process involving Office of Research leadership was put into place for research activities that would otherwise receive IRB approval in accordance with federal regulatory criteria but for which social distancing is not always feasible. Before study teams are notified of IRB-approval of their studies, ancillary review provides University leadership with a formal means to consider whether to allow studies for which social distancing for one or more study activities is not practicable. Such studies have included blood draws, affixing wearable devices or equipment, and EEG or other procedures where a researcher must have some physical contact with a study subject. The ancillary review process was easily incorporated into the EPMS and involves an additional review step after IRB approval. OHSP/IRB staff submit an ancillary review request that is electronically routed to research leadership (which also sends an email communication to the ancillary reviewer outside of the EPMS indicating a need for ancillary review and providing a link to the EPMS to obtain study details). The EPMS request highlights those specific study activities for which the University's social distancing requirement is not feasible but for which activities the study team has documented justification or rationale. Research leadership documents their review decision within EPMS, which becomes part of the IRB record as an institutional review under section 46.112 of the applicable federal regulations. OHSP then conveys

the ancillary review decision as part of the IRB review outcome for the study that is communicated to the study team.

Conclusion

Development and implementation of COVID-19-related requirements for human research studies occurred in tandem with the University's early cessation of in-person research activities and required that the OHSP/IRB pivot away from other priorities at the time, including staff development, recruitment of new IRB members, and updates to existing policies and templates. With University leadership and the Board of Governors' policy and support, there were no barriers in enforcing COVID-19-related requirements for human research. Early and constant communication and messaging, dissemination and ready availability of instructions, guidance and templates, use of remote technology and an EPMS, and a careful process for conducting COVID-19-related reviews, has clearly facilitated the handling of human research review in the difficult and challenging COVID-19 environment that early on besieged the University. In some respects, the altered review process has become routinized, which for better or worse, may be the new normal for a while longer.

Warping of Time

Carol A. Pech

Nearly a year into the pandemic, we are too familiar with the twisting and blurring of time it has brought us. I find it hard to remember how our sense of time worked before COVID crashed over us. If you happen to be a musician (guilty), you know how to read through new-to-you complex pieces of music to see how it goes—slow here, fast there, tricky in places. Although I had the same instinct in the run-up to the pandemic, we had no such luxury. We played as we went, and this is part of that story.

Prelude

I would not characterize myself as a prepper, but so I become by early February. I advocate for getting ready, and my colleagues ask whether I think we truly need to start preparations now. The virus isn't in our community yet—or so we think. My response is that I believe so, since if the virus comes—and we do not know that it is already in our midst—my sense is events will unfold quickly. This is the best guess I will make about time all year.

Shortly afterward, leaders further up the chain of command ask for our continuation of operation plans (COOPs). I work in the institutional review board (IRB) office at a large research university with an equally large human participant research program. IRBs of our size always need to be in continuous operation, so the COOP exercise seems like administrative busywork, although at least it gives us the sense that we are actually preparing. For exactly what, though, we have only a vague idea.

This changes in mid-March when, while searching for Covid resources on other IRB websites, I fin a west coast research university with a list of FAQs for researchers. As we start liberally borrowing from them, we meet with their IRB director for advice. What we hear: figu e out how to implement the new public health exception in the federal regulations, which we have not yet used. Prepare for an influx of emergency, one-time use requests for remdesivir, presuming we can get any. Working remotely and handling a flood of information will stress staff, with no easy fix. Figure out how you will obtain informed consent from patients in isolation—we have never had to think this through. Researchers will have a ton of questions. Get ready. And good luck.

Around the same time, our biggest viral research lab reaches out about collecting samples from COVID-positive patients since we already have community spread. This is sobering news.

A week later, I send the email to our office telling everyone to go home for the duration, now going on a year. And another week later, campus leadership announces that face-to-face interactions with human subjects that are not directly therapeutic must stop. All research procedures that can be done remotely must be done so. And our ordinary sense of time at last slips away.

Presto

The blurring of time accelerates in April and May. We are drafting and posting guidance for our researchers as quickly as we can—often every day, sometimes twice a day. As forewarned, our office is field ng an almost overwhelming number of questions from study teams. With leadership on the clinical trials side, we coordinate on reviewing the influx of Covid studies that need approval yesterday. Staff are indeed stressed and to help us try to keep pace and informed, I send out daily COVID updates—today's new FAQs, news from the FDA, COVID studies in the pipeline. And I always include a signoff to be well, whatever that means.

Despite our best efforts to stay on top of everything, we are scrambling, particularly with issues we have never faced before. Do we have an FDA-compliant system for documenting informed consent? We do not, so we work on getting that moving. Do study teams need to submit changes to their protocols to re ect pandemic-related modifi ations? Sometimes yes and sometimes no. What online platforms for study visits are HIPAA-compliant? Two, and not the ones that study teams want to use most. We press campus on that, too. Do we need to report halts in enrollment? Please, please, do not. And many other questions, the answers for which we are both making up on the fly and relying on our colleagues across the country to help nail down. And—bless them—the FDA issues guidance we can shelter under. And messaging from regulators to IRBs is, basically, do the best you can.

We briefly catch our breath before discussion of resuming face-to-face research for non-therapeutic studies begins. And with it, another flurry of questions, consultations with other IRBs, and posting of guidance starts all over. What about PPE for participants and study teams alike? What about infection control measures? How does the IRB review and approve plans we are not well suited to evaluate? How much hustle do we have left to manage this? Mercifully, and for the first time in the pandemic, we do not have to add more to our plate, and other entities on campus take the lead. And we can slow down, although at the same time, we are still moving quickly. Time folds and twists on itself.

Coda

Our list of Covid FAQs is now stable. Most higher volume research groups are in sync with our guidance. I stop sending out daily updates to staff by late June. We are in the groove of remote work and IRB meetings. We continue to provide highly responsive service to our researchers. We are grateful for the support of our colleagues, both internal and external. We are thankful to our research community for the work they continue to do and their willingness to partner with us as we sifted through more questions than we can count.

Time is not back to normal, though. If anything, we are in suspended animation, waiting. How and when will vaccines impact our research community and IRB operations? When will we go back to the office and what will that even look like? Will the predicted bleak midwinter come to pass? With new variants of the virus circulating even now, will we ramp down again?

As at the start, we have no idea how this will go.

Research on COVID-19: Story from the Kenya Medical Research Institute

Kebenei Enock Kipchirchir

The first case of COVID-19 was confirmed in Kenya in March 2020. The announcement made by the Ministry of Health created panic

in the country and many changes in the normal way of living. The Government of Kenya issued a number of directives to curb the spread of the disease. The containment measures affected all sectors of the economy, including health. The Kenya Medical Research Institute was at the epicenter in responding to the pandemic through testing, surveillance and systematic investigation into the novel virus. Scientists at KEMRI responded to the various calls for research proposals on COVID-19.

The KEMRI's Scientific and Ethics Review Unit (SERU) is a unit that houses the Research Ethics Committee (REC). All research proposals must be reviewed and approved by the ethics committee before study implementation. Prior to the announcement of the first case of COVID-19 in Kenya, KEMRI SERU operations were purely paper-based. We had to shift to the online submission system and virtual REC meetings to curb the spread of the killer disease. We had to respond to the increased number of proposals for review and keep the disease at bay. To date, the KEMRI SERU has reviewed and approved more than 50 new proposals related to COVID-19.

The new normal of providing research oversight with strict adherence to the various guidelines of curbing the spread of COVID-19 came with a fair share of challenges. The problems in reviewing and overseeing COVID-19 research ranged from administrative to logistical issues. Members of staff at the research regulation arm had to stay and work from home. We experienced challenges such as intermittent internet access and lack of equipment like computers, scanners, printers, and photocopiers at home. All research proposals on COVID-19 were reviewed on a quick turnaround basis. The challenge to this is to supervise staff who are working from home and ensure that they respond to urgent requests. All requests for ethical reviews were received through e-mail. There was a challenge in putting all documents in a centralized location because staff could access the email at home. Documents management requires a centralized system that can be accessed remotely. An upsurge in the number of expedited review requests strained the limited resources in the unit.

Our work involved issues of autonomy and respect for persons who test positive for COVID-19 and researchers want to use their samples for different research purposes. Human beings enrolled in research should be treated as autonomous agents regardless of the situation at hand. No one should disrespect the rights and welfare of research participants in the name of responding to the pandemic. Researchers must ensure that they seek informed consent from COVID-19 patients to use their collected samples for research purposes. The Research Ethics Committee has also found it difficult to conduct site monitoring visits due to travel restrictions. We have to rely on self-reported protocol deviations, violations, safety, and other notifications received from principal investigators to conduct passive monitoring of the study.

The KEMRI SERU made necessary adjustments to accommodate urgent review of COVID-19 research proposals during this period of the pandemic. One of the special accommodations made is the expedited review of all COVID-19 research—the unit endeavors to respond to the investigators within ten days. We have not increased the number of staff but considered motivating them further. The institute issued Telkom cards with sufficient internet bundles to allow the staff to access the Internet from home. The reviewers were also given a token of appreciation during this period. Expanded access requests are being reviewed jointly between REC and the national regulators. Initially, studies were reviewed by the REC and the national regulator sequentially. However, during this period, some studies have been reviewed jointly/concurrently by the national regulator and the IRB to reduce the turnaround time.

The review of an increased number of COVID-19 research proposals has taught us many lessons that we can share with other IRBs. It would be helpful to have separate reviewers for expedited reviews and motivate them during the pandemic. Such members will be on call anytime you have an urgent request to review studies responding to the pandemic. To the researchers, the welfare and safety of participants who test positive for COVID-19 remain paramount. It is advisable to observe containment

measures and seek appropriate consent from such participants or their family members.

Our experience of reviewing and overseeing COVID-19 research tells us that it is sometimes tedious to review protocols that are developed in a hurry. It is important to have peer reviews of COVID-19 research protocols before submission to the REC for ethical clearance. It was noted that many researchers did not comply with standard operating procedures due to the urgency to submit and start research work. It was noted that checklists were not being followed to the letter.

Commentary
IRBs During COVID-19: Tried and True

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Abstract. The COVID-19 pandemic threw health care logistics and clinical research processes into disarray. This collection of narratives describes the challenges faced by IRB administrators, staff, and committee members as they navigated the SARS-CoV-2 pandemic. The authors transitioned to remote meetings, adjusted to ever-changing information, and untangled the ethical implications of supporting open studies while making room for an influx of new protocols that addressed the pressing public health emergency.

Funding. The work to put together this symposium was supported by the National Institutes of Health [3R01AG058254-03S1 (James DuBois, principal investigator)].

Keywords. Bioethics, Clinical Trial, COVID-19, Human Research, Human Research Protections, Institutional Review Board, Medical Ethics, Narratives, Research Ethics, SARS-CoV-2

The unexpected global spread of the SARS-CoV-2 virus was unprecedented. While the rate of infection and mortality projections were shared concerns, retailers worried about business, employees wondered about their next paychecks. Parents and children were alarmed about the loss of classroom time, and state and local governments struggled mightily with the logistics of managing a public health crisis of this magnitude. There was immediate attention on health-care providers, scientists, and drug developers as the frontline defenders of our communities. We expected medical personnel to treat the emergent sick, researchers to find an answer, and pharmaceutical companies to mass-produce the solution.

Wedged between the scientists and the drug developers are legions of largely unrecognized but vital facilitators of the therapy-development process—the Institutional Review Board (IRB) administrators, staff, and committee members. They are taken for granted, much like the street system in every town, but they are literally the road upon which science travels to reach the answers to our health questions. These twelve IRB narratives describe how their normal lives and human research protection processes were upended by the COVID-19 pandemic and what happens when what might be considered a staid and administrative-heavy occupation becomes super-charged by the realization that it is a crucial component in the fight for continued life on this planet.

In this commentary, I will remark on the stages of IRB experiences that can be characterized as "panic," "initial response," and "settling in." Then I

will offer a discussion of three themes that underly the entire journey, and how these are related to principles that guide the practice of ethical research.

Panic

> *". . . urgent rethinking of the full scope of our human subject research program and its oversight." Edith Paal*
>
> *"I watched as panicked physicians, patients, and media outlets turned to the research community for answers, desperately hoping cures, vaccines, and preventive measures could be produced." Walter Dehority*
>
> *". . . [Staff] truly felt their lives were at stake" if they were physically present in the office. Stephanie Juell*

The above are not the sort of statements one would normally associate with the review of clinical research studies. In my twelve collective years on IRB committees, my fellow committee members and I, and our IRB staff, understood that our work seemed uninteresting (and even dreary) to family and friends who asked polite questions. Methodical paperwork, compliance checklists, decision pathways, record keeping, ongoing training, meeting logistics, and subject interactions—all of these intersected with ethics in a way that was difficult to explain to outsiders. We might admit to elements of the IRB "grind," but as insiders, we knew the importance of our work—and this kept us motivated. Imagine the shock to find that normal IRB operations were suddenly the gateway to the search for treatments for and protection against a virus that was attacking the planet! As Doherity mentions above, *all* eyes were on the IRB—or at least pointed in that direction. The authors share that the scrutiny was keenly felt.

These narratives describe being pulled in many directions during the weeks of March 2020. They use the words "terror," "urgency," "overwhelmed," and "weary." These authors wondered: How do we continue to work safely? Is remote work feasible? Will confidential data remain secure? Are there aspects to an ethical review process that *must* be done face-to-face? Does the pandemic dictate modification of requirements and timelines? They also asked: What exactly *is* our work? How do we manage existing open protocols and applications already under review? How should IRBs weigh the unknowns of COVID-related research questions against a dire public emergency? Who decides the parameters of all the above? These IRBs didn't know how to gauge if they were acting too quickly to be safe or, conversely, too slowly to save lives. There was "self-imposed pressure to make experimental therapies rapidly available," says Doherity.

The panic was elevated by confusion regarding who had the authority to modify the normal sequences of operation. While the public struggled to untangle inconsistent federal, state, county, and city-wide messaging—IRBs wondered who define the boundaries and pace of their immediate actions. "Investigators were confused and not sure whether they could move forward or not. They needed direction," says Hallie Kassan. And Paal notes that "The IRB fielded many queries . . . but these decisions were made at the institutional level . . ." John Tupin describes "unavailability of the institutional decision maker and no process for emergency delegation." And finall , "We HRPP folks are compliant by nature," says Juell. "We want to do the right thing. And we want to follow the rules and the laws," but she was distressed by the initial tension between "following the rules" and "doing the right thing."

Initial Response

> *"Small, uncontrolled studies began to appear in the literature, many bypassing peer reviews, feeding scraps of pilot data to a frightened medical community." Walter Dehority*
>
> *"Most of the dilemmas I faced while reviewing COVID-related research can be attributed to the seemingly endless review of overlapping research." Sara Griffi*
>
> *"We needed a rapid turnaround time for this review. The struggle was giving the IRB members enough time to perform an adequate review." Hallie Kassan*

Mid-March 2020 is referred to, with somber awe, as a time when "the emergency hit," "we grappled with our personal fears," and "rumors started flying." "I wept as my students and I discussed the suffering

that would likely ensue," shares Jennifer Randles. But after the initial shock, there was a universal gathering of wits. IRB administrators and staff are nothing if not problem-solvers, and they worked tirelessly with investigators and committee members to keep the workflow moving as everyone transitioned to remote interaction. Trial and error led to frustration. Sujatha Sridhar shares that her first online IRB meeting was a disaster, but after a few tries, "what had appeared to be an insurmountable challenge turned out to be an advantage." Brian Moore notes in his journal that online IRB "discussion and vote are consistent with our in-person meetings, so we adjourn satisfied that we have fulfilled our ethical, moral, and regulatory obligations."

Flexibility was the key for untangling logistics, modifying policies, and juggling new data. "Flexibility created agility," says Ann Jonson, but it was not the answer to everything. Griffin shares that "Most of the flexibility [for consent] that has been granted during the pandemic is applicable only to COVID-related populations . . . researchers who continue to conduct research in non-COVID populations have been left with few options." Juell warns that "Pandemic work . . . requires flexibility and creativity in terms of meeting regulatory requirements but it is crucial to remember that the regulations themselves serve a larger purpose." She goes on to describe an ethical balancing act, wondering about "expectation and responsibility; law and ethics; written law and the intent of such laws." Edward De Vos points out, "If in the short term we assign higher priority to minimizing risk, we risk paying less attention to equitable distribution of burden and benefit." Dehority speaks of deliberation "sacrificed on the altar of speed and efficienc ." These are not flippant depictions of administrative mindset but are indications that skilled professionals felt torn between opposing forces.

Settling In

"Partly due to concerns raised by IRB members and staff, a committee was established on an institutional level that monitored all projects seeking to enroll COVID-related populations." Sara Griffi

"The decision makers felt very strongly that we should try to limit our trials to randomized controlled trials, in an effort to put the best science forward." Hallie Kassan

"We quickly realized that sending multiple emails to our research community created confusion instead of clarity. Instead, we developed an intranet site and a Google Drive folder to share information with our research community." Sujatha Sridhar

As weeks turned to months, programs developed strategies to meet their new needs: streamlined application processes, especially trained "consenters" for hospital-isolated patients, rubrics for decision-making, small committees on call, and automated emails in response to frequently asked questions. De Vos notes that IRBs are charged with assuring that investigators and IRB members are adequately trained to protect human subjects—and that this responsibility did not change during the pandemic. It is no surprise that compliance issues were in the forefront of everyone's mind, and many authors discussed their learning curve dealing with Emergency Use Authorizations and the need to assign expert "teams" to address this.

In the majority of the narratives, the tone of the authors changes about halfway through. Distress takes a back seat as they describe the ways that staff and committee members collaborated to keep their research review ethical and timely. They are "proud," "dedicated," and "thoughtful." Our offic worked "Herculean hours," says Paal, and "we are especially proud of the creation and approval of our expanded access protocol." "We recognized that it would be important to . . . identify trials most beneficial to our patients and that had the highest chances of successfully being done here in our institution. A COVID-19 clinical research workgroup was formed," relates Sridhar.

With experience under their belts, came other realizations. "Studies, which several weeks prior we hurriedly approved during emergency IRB meetings, were now being hurriedly assessed for closure or suspension due to newly identified risks in the rapidly expanding medical literature," notes Dehority. John Tupin makes several good points: Telemedicine is a good strategy but "what about

rural patients, the homeless and impoverished, or my 86-year-old father who uses his laptop as a paperweight?" How HIPAA compliant are all the new online transmission and storage tools that we are using? And importantly, "I worry that some of the actions we took will result in a disqualification of collected data."

These narratives were written six to eight months after the onset of the pandemic. There are unique touchpoints in each journey, but the authors' personal and professional growth and the evolution of their affiliated programs are evident as the stories progress. Three themes are woven into the thoughts, actions, and responses: the impact of stress on the human element of research review, the importance of communication, and the value of common-sense application of existing ethical principles.

The Human Element

> *"Our Board members and IRB staff were exhausted, scared, frustrated, overworked, and overwhelmed. Our conference rooms had been turned into hospital rooms. The library had been turned into a medical storage facility. Clinicians were working overtime all the time and trying to catch naps on chairs. And our frontline healthcare workers were getting sick. Some passed away." Stephanie Juell*

> *" . . . employed mothers . . . pushed to the brink at home themselves as the already thin lines between work and home blurred even more . . ." Jennifer Randles*

The authors discuss many layers of stress. New Yorkers who lived through the first terrifying wave of the crisis felt like they were "on top of each other" as they traveled to and from work before the decision was made to operate remotely. Salt Lake City was doubly traumatized by a mid-March earthquake. One author was stuck abroad after travel became restricted. Parents juggled homeschooling as they met remotely for IRB meetings, commandeered kitchen tables and bedroom corners for makeshift offices, and tried to maintain healthy personal lives while they felt the weight of responsibility. "The world was turning to the research community for answers," says Dehority. The stakes were high—the difference between life or death for patients. "I could not allow myself to succumb to the pressure of desperation," declares Juell. "It was difficult to disapp ove proposals," adds Sridhar.

Dehority offers a thoughtful discussion about therapeutic misconception and misestimation, noting that incorrect assumptions about potential benefit are largely grounded in hope—and affect investigators, staff, and institutional officials, as well as patients. He worries that hope might have prevailed over scientific caution in his own mind, but notes, "Such insight, more easily achieved after the fact, is difficult to rely upon when a pandemic finally reaches your borders and comes knocking on your door." And the moment when most would welcome—even require—the professional and personal support of in-person work environments, and opportunities for serious discussion about the ethical implications of pandemic-era decisions, everyone was ordered to stay home. Jennifer Randles says, "We are social beings primed for empathy and compassion, and we feel the collective stress and strain of the pandemic, even if our lived experiences are steps removed from its worst outcomes."

The authors share different versions of the same challenge: they are fundamentally concerned with promoting the immediate ethical review of clinical research, while simultaneously managing misgivings about their own safety, that of their loved ones, and, even, existential reflections about global danger. Juggling so many layers of subjective and objective stress is certain to have impact on quality of decisions and interpersonal relationships, and as professionals, they know this. Readers can see them struggle to access their own skills and expertise, while trying to discern the larger context of their responsibilities. We watch them second guess themselves, before they ultimately settle on two guiding principles, which I identify as "communication is paramount" and "existing principles hold."

Communication

> *" . . . the pace of communication . . . was not keeping up with the swiftness of change." Sara Griffi*

> *"The challenge was how to implement these changes in a compliant way without overloading the IRB and*

the IRB member-reviewers, and avoid confusing investigators by communicating clearly to faculty, staff, and students." Joan B. Cobb Petit

"Communication within research administration and to the study teams . . . and between research and clinical care teams is essential." Hallie Kassan

"Communicating often and clearly with everyone is key." Sujatha Sridhar

The parameters of each author's role, and the ways they interacted with other members of their team, were diminished, expanded, distorted, or reframed. Tried and true networks of communication, already fine-tuned to accommodate the intricate process of research review, were dissolved or rerouted. New data about the virus, short-term exploration for treatment, and long-term plans for prevention changed, sometimes, on a daily basis. No matter what aspect of the pandemic this new information related to, the practical logistics and ethical processes were affected. Decision pathways were like chains of dominoes—a choice at one end of the row instigated a cascade of action. It was important to make sure the dominoes were lined up, that the pattern was orderly, that momentum was maintained, that the pieces fell in the right direction, and that the right person pushed the best tile. Each program eventually found what worked for them: automatic email responses about specific topics, dedicated websites that outline new guidance, FAQs and live Google docs, regular memos from leadership, frequent check-ins between task-specific committees, and weekend or late-night calls. "Staying connected is important to assure efficiency of processes, says Kassan. And Sridhar shares that, "We learnt pretty soon that it was important to communicate daily, and sometimes several times a day . . . [and to] and listen to voices from as many groups of people as possible . . . Being transparent about the process was helpful in gaining the trust of the research community as we all navigate these challenging times together and learn together."

The point here, is that these IRB teams realized they were a conduit of information, and the intersection between several branches of response to the pandemic. Already accustomed to serving as a bridge between competing agendas and stakeholders who often did not speak the same language, they were able to focus their energy on the most crucial of components for successful movement forward: efficient pathways of communication. They intuitively knew and/or logically came to the conclusion that their work required collection and dissemination of accurate and timely data, and it was up to them to make sure others understood the content and acted on the import.

Existing Principles Hold

"Respect for personhood, beneficence, and justice are collective promises that reflect our core humanity . . . [and these] guide us along a path to coping with these challenges and facing the daily dilemmas of the COVID-19 era." Jennifer Randles

"Maintain confidenc . . . adhere to principles . . . protect subject rights . . . act as a leader . . . be consistent . . . publish guidelines . . . stay human . . . practice selfcare . . ." Stephanie Juell

The dire circumstances of the pandemic inspire compassion for the suffering and dying, and anxious desire to spring into action, but this "new situation" does not mean we need "new rules." The old rules—our existing tradition of ethical research practice—are still valid, and in some ways, even more important, given the magnitude of potential harm and ethical dilemmas we face as we try to address this global emergency. How should an IRB deal with the therapeutic misconception and therapeutic misestimation that Dehority mentions, when it attacks subjects *and* investigators? How should IRB committees guard against the ways that widespread "images of death" might affect a valid consent process? The answer is not to invent *new* strategies, but to wield, with confidence, the tools that have already stood us good stead.

When Edward De Vos worries about rural populations having access to vaccines or telemedicine, this is not based on a "new" theory of justice. And when he questions whether confidential information will remain secure spread over a patchwork of internet access points, or whether remote research might not be as carefully validated, he is not inventing a new standard of HIPAA or novel Common

Rule standard for science. These are existing tenets of ethical research practices. Time and time again, we see in these narratives where the authors are shocked at first, but then catch their breath and realize they can trust their common sense to use the tools they are familiar with: respect for persons, beneficence, justice, best practices for consent, and the flexibility built into the federal regulations. Despite the urgency of the COVID-19 crisis, the corner stones of research ethics still held.

Conclusion

The latest edition of *Institutional Review Board: Management and Function* (2021) reminds us that ethical reasoning involves identifying the moral question, understanding the facts, drawing on ethical frameworks and principles, weighing the various moral considerations, and making a considered moral judgment. "While the IRBs process," the editors write, "rarely involves this kind of step-by-step moral reasoning, knowledge of ethical principles and reasoning processes can be key in navigating complex situations or those not covered by the regulations." (p.4)

In the face of novel crisis situation, the authors fall back on the ethical principles they are accustomed to and use their practical know-how to implement them. Moore writes that the pandemic emergency "shone a light on many areas of weakness," and others describe modifications that "needed to be made anyway." As a collection, these stories describe well-trained professionals taken aback by a crisis, but "having emotions isn't unprofessional. It's human," observes Juell. The IRBs catch their stride—and they take care of business because, as we are reminded by Doherity, "Interventions without proven clinical benefit need clinical trials." Finally, as much as I would like to close this commentary with a bit of original wisdom, Jennifer Randles offers what I believe is the underlying sentiment of this collection: "Respect for personhood, beneficence, and justice are collective promises that reflect our core humanity. As such, they are the best guide for how to navigate this crisis—in our IRB offices, our classrooms, our research encounters, our homes, and our relationships with one another."

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Commentary
Protecting Research Subjects During a Pandemic

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Abstract. This commentary discusses twelve stories in which people who are involved in institutional review board (IRB) administration or serve as IRB members tell the stories of how the COVID-19 pandemic affected their work and lives. Among the aspects of these stories it highlights are the need to focus on the well-being of the institution's employees, and how issues involving protecting vulnerable subjects might relate to current policy debates about underserved communities. The final portion of this commentary focuses in particular on how one might measure success for a program in protecting its research subjects during a pandemic.

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Keywords. Research Ethics, COVID-19, Pandemic, Human Research Protections, Ethics Committees, Narratives

"There are eight million stories in the naked city. This has been one of them." So went the tag line in the 1948 film *Naked City*.

Nearly seventy-five years later, we find ourselves dealing with a pandemic that, in one way or another, has affected the lives of everyone on Earth. There are now eight billion stories that might be told. In this issue, we find twelve stories about how the COVID-19 pandemic has affected the lives of people working in the field of protecting research subjects. This field is partially defined by a line relating to whether particular information does or does not constitute generalizable knowledge—a line that has been fairly subjected to a great deal of criticism. That circumstance can remind us to be particularly careful before concluding that these twelve stories can be generalized to broader conclusions. Regardless, as with *Naked City*, that doesn't make each of these stories any less worthy of our attention.

Lives, Shaken

Ann Johnson perceptively titles her essay with the single word "Shaken," and the reader quickly comes to appreciates her double meaning: as she and her

Salt Lake City colleagues in mid-March 2020 began dealing with the effects of COVID-19 on their lives, they also had to deal a few days later with the literal shaking produced by a 5.7 magnitude earthquake.

The metaphor of shaken lives permeates many of these essays, and reminds us of what might otherwise get lost in a discussion of how the pandemic affected the operation of IRBs. Like any other administrative entity, an IRB can only function well if the people who run it and serve on it are able to function well. Thus, a prerequisite to an IRB doing its job of protecting participants in research is that its own people receive adequate protection.

Hallie Kassan tells the story of a large health care system in New York State that over time ended up treating a substantial percentage of the patients with COVID-19 seen in that state. By March 12, 2020, "it was clear that staff did not feel safe coming in to work any longer." That same day her IRB system decided to switch to remote work. It was only after "the staff were settled" that she was able to turn to all of the other issues relating to keeping that system functioning during a pandemic.

Stefanie E. Juell eloquently writes about what took place in her New York City program, as she and her department director grappled with their own "personal fears and uncertainties" about the virus. Juell writes, "we were also attempting to define the limits of our ethical obligations to our staff, our institution, and our community." Even though she knew her staff was capable of working remotely, "higher-level leadership was reluctant to permit such a dramatic shift." The result was that her office "was increasingly inhabited by staff members on the verge of tears. Some even considered quitting because these (mostly women) truly felt their lives were at stake for the purpose of being physically present in the office." Juell describes this as a dilemma between "following the rules" and "doing the right thing," as she was torn between supporting her institution as a whole, versus the people who worked for her.

Of course, Juell's program did indeed quickly switch to remote work for IRB personnel. That switch similarly took place for each of the other programs described in these stories. That the authors pay such great attention to this change is but one reminder of the importance of an institution taking care of its own people, as a prerequisite to taking care of others.

Protecting the Vulnerable

Apart from the pandemic, one of the other themes playing a major role in current policy-making in the U.S. is a special attention to the interests of marginalized people. In many ways, this group has been especially harmed by the pandemic, bearing more than its share of harm, in terms not only of death and morbidity, but also of economic impact.

Protecting the vulnerable—particularly those who are vulnerable to coercion or undue influence is an explicit part of the federal rules for protecting research subjects. That concept shows up in three places in the regulations: 45 CFR 46.107(a), relating to IRBs having members who are knowledgeable about those groups; 45 CFR 46.111(a)(3), relating to the need to equitably select subjects, which can involve determining that vulnerable subjects have neither been under-included (thus being deprived of the benefits from the new knowledge) nor over-included (thus suffering more than their fair share of the burden) in research; and 45 CFR 46.111(b), requiring appropriate "additional safeguards" to be in place to protect vulnerable subjects. Many of the stories in this collection touch upon this topic, and they do so in a variety of ways.

Edith Paal writes of her program's success in assuring that there is expanded access availability for unproven COVID-19 treatments for both prisoners and those who cannot speak English. Juell observes that "[m]any of our patients are some of the most vulnerable: families living at or below the federal poverty line, undocumented individuals, families without easy access to fresh, nutritious food, and communities struggling with systemic racism and severe financial stressors." Edward De Vos notes how "[h]istorically underserved and marginalized populations are disproportionately represented among the poor, and poverty may limit the ability of some to participate in online research." John D. Tupin writes about his institution's experience with research on telemedicine, and

the difficulty in reaching particular underserved communities: "what about rural patients, the homeless and impoverished, or my 86 year-old father who uses his laptop as a paperweight?"

Jennifer Randles personalized this issue, writing about her multiple roles as a relatively new IRB chair, in addition to being the Sociology Department chair and a principal investigator involved in ethnographic research on families in poverty. As the employed mother of a 4-year-old, she "personally got no fewer than 10 requests to participate in research on how employed parents and caregivers were coping with the dual challenges of essential in-person work or working remotely at home while homeschooling and providing 24/7 childcare." And her own life experience has been invaluable in helping her understand how to best "interview marginalized mothers about sensitive topics, including poverty and struggles to provide for their children's basic needs."

All of this reinforces and demonstrates how this aspect of protecting research subjects is very much "of the moment" in terms of its ties to the broader movement taking place within our society.

Measuring Success

By a wide margin, these are stories of success, with upbeat endings. There is no braggadocio: merely a modest recognition that, under extraordinary circumstances, their people had an important role to play in our moving forward from this epidemic, and they managed to do their jobs very well—often going to extraordinary lengths to accomplish that. One should take the time to reread each of the stories and pay particular attention to the eloquent descriptions of how employees ended up going far beyond what might normally have been expected of them. These messages of overcoming adversity bring to mind John Gorka's comment in his song "I'm From New Jersey": "If the world ended today, I would adjust."

And adjust they did. Indeed, if there is a dominant theme in the various litanies of success, it is that of flexibilit , a term which appears in half of the essays. Brian Moore tells us that "the underlying concepts of respect, justice, and beneficence have shown through," but they now have a greater appreciation of the need for being "flexible in accommodating" the needs of study participants. Joan B. Cobb Pettit attributes her institution's success in significant part to its flexibility in applying the regulations. Sara Griffin writes that, particularly with regard to the conditions relating to obtaining consent, there was a strong desire on the part of both researchers and IRB staff to be as flexible as possible. Sujatha Sridhar observed that her institution enabled a new process for obtaining consent remotely, though pointing out that it would be "as robust as an in-person consent process." Ann Johnson comments on the particular need for flexibility regarding the requirement that a single IRB has the responsibility to review a multi-site study.

In looking at the specific indicators cited for success, many of them seem to relate to procedural goals, being able to accomplish what they did before, but under a new reality: implementing new ways to conduct IRB meetings virtually; creating new ways to obtain informed consent; allowing studies to take place with fewer in-person contacts; approving COVID-related research at a much faster pace than had ever been done for other types of research.

Another Measure of Success

Which raises a question: what about the *substantive* decisions that were made? Do those decisions tell us anything more about how good a job we are doing in protecting subjects? Consider, for example, the role of IRBs and human research protection programs in enabling the use of unapproved products as treatments for COVID-19. Paal, for example, writes of the "drafting from scratch of an expanded access protocol" for an experimental treatment, and how they were "especially proud" of that. Juell's system was "inundated by emergency use requests." "[W]e all understood that our ability to quickly respond to questions from clinicians about the use of non-approved drugs might very well be the difference between life and death for patients in need of such treatments. I felt personally responsible for the lives of patients I never saw."

Was it not an unalloyed good thing to be making these new treatment options—sometimes in research studies, sometimes as part of clinical care—available to very sick COVID-19 patients who likely had few other choices? One of the writers tells a story suggesting otherwise. Indeed, for IRB chair Walter Dehority, the experience of COVID-19 appears to have left him with a cautionary attitude. The concept of therapeutic misconception played center stage in his thoughts: "the failure to appreciate the distinction between the goals of research, which are to collect data to contribute to scientific knowledge, and the goals of clinical medicine, which are to improve the health of patients." He goes on to tell a story of "panicked physicians, patients, and media outlets turn[ing] to the research community for answers, desperately hoping cures . . . could be produced. . . . Small, uncontrolled studies began to appear in the literature, many bypassing peer review, feeding scraps of pilot data to a frightened medical community. Clinical trials materialized overnight."

Given how desperately the COVID-19 patients at his hospital wanted cures, he stayed awake for several nights before an IRB meeting, worrying: "Would any of our potential research subjects actually consider the warnings in a consent form about the possible risks and lack of proven benefit for an investigational therapy when offered the chance to participate in a COVID-19 clinical trial? Particularly after these potential study subjects had viewed the same images of death in New York that I had?" And he notes that this same therapeutic misconception could affect IRB members, including himself: "a self-imposed pressure to make experimental therapies rapidly available to our patients, and to quickly facilitate the opening of our hospital to clinical trials to do our part to aid a community (and nation) in crisis."

He cites one example familiar to us all: "[D]id the medical community really need 104 trials of hydroxychloroquine that April (all presumably IRB approved, two from our institution), many of which were single-site, underpowered, or uncontrolled studies?" His conclusion: IRBs need to balance their "genuine desire and responsibility to rapidly approve clinical trials that will facilitate the study of novel drugs, vaccines, and diagnostic modalities that may produce urgently needed data" against "an equally important need to slow down during what is a time of relative urgency and critically evaluate each proposed trial in order to ensure the protection of the human subjects enrolled within it, even if that means asking difficult questions that may delay the start of a trial."

Dehority's concerns find echoes in what Juell writes about her own experience as a reviewer of a hydroxychloroquine trial: "[I] expressed concern that there was insufficient evidence in the protocol to convince me that the benefits outweighed the risks associated with the drug, especially for participants with cardiac conditions. I was promptly and publicly shamed and questioned by a scientifi board member who snapped, 'Isn't that exactly what we're trying to figu e out!?'"

There is also an important ip side to Dehority's concerns that is very much at the core of therapeutic misconception, though he doesn't appear to bring it up: what about the scenarios in which the off-label use of some drug might indeed be in a patient's best interests (even given the uncertainty about its efficacy), so they might prefer to directly receive it as clinical care instead of being in a trial (which might only provide them a 50% chance of receiving it)? Though, I suspect, Dehority may not view this as a big problem, given his sense that the major concern was the over-hyping of unproven treatments, others have indeed been concerned about this scenario.

One of the most compelling stories about the blurry line between research and clinical care during the pandemic—Susan Dominus's *New York Times* account of arguments between researchers and clinicians at a major New York health care facility—deals with this very scenario (2020). Among other things, she described a physician who wanted to remove her patient from a blinded COVID-19 clinical trial where the participants were randomized between higher and lower doses of an anticoagulant. The patient had recently had a cardiac arrest. Given that development, the physician now felt that it was in the patient's best interests to be receiving the higher dose, so she was considering removing the patient from the trial.

The lead researcher for that trial was participating in the discussion by videoconference. He had previously had "heated words" with the doctor, unsuccessfully trying to talk her out of doing that. As the clinician told him, "She had to rely on her clinical judgment and believed that it was unethical to wait for more information. How could researchers dictate care to a doctor right there at the bedside, especially when a patient's condition was so dire?"

But the researcher had remained unconvinced. During a subsequent in-person meeting among clinicians, where he was participating by videoconference, he again tried to make his case for the wrongness of what that one clinician wanted to do. He talked about the importance of high-quality randomized trials, and "the risks of trying experimental treatments without them." "Relying on gut instinct rather than evidence, he told them, was essentially 'witchcraft.'"

Upon hearing those last words, one of the clinicians—even though she was only participating by videoconference—felt a "chill in the air."

Dominus's article touched upon a core issue surrounding the conduct of some COVID-19 treatment research in the U.S., where the treatments being tested were otherwise available to be prescribed as part of clinical care (i.e., outside of a research trial) (2020). Why was it that the U.S. appeared not to be enrolling that many patients into such clinical trials? Some have argued that too many physicians were providing these unproven treatments as part of clinical care, thus cannibalizing the ability to enroll people in the trials (Magnus, 2020). Indeed, the arguments have gone so far as calling for changes to the rules of medical ethics (London, 2021).

As I read these twelve stories, I couldn't help but wonder what their authors might think of this dilemma. And more importantly, how might the actions of their IRBs have influenced the outcomes in one way or another in similar scenarios, particularly with regard to what patients were being told in consent forms and consent discussions? Were the consent forms for randomized trials fully upfront in explaining how and when it might be in a patient's best interest to directly get an unproven treatment as part of clinical care, instead of only getting a 50–50 chance at it in the trial? And on the flip side, picking up on Dehority's concerns, might the consent forms in expanded access (non-research) scenarios sometimes over-promise the likelihood of benefit? Unfortunately, all too commonly, it isn't that easy to get access to the consent forms for clinical trials, and so I—and you, the reader—are left to merely wonder about this, and not know.

The real world sometimes provides us with unexpected coincidences. One of the twelve authors, Hallie Kassan, is the director of the program for protecting research subjects at the institution that Susan Dominus wrote about. Oh, to be able to learn her thoughts about all of this. Or to have been a fly on the wall among gatherings of her colleagues, including the IRB members, while these events were taking place.

Conclusion

Like the best story-tellers, these writers left me wanting to hear more. And there really is so much more to figu e out about how to deal with a pandemic, including in particular thorny issues relating to unproven treatments, and an IRB's role in making sure that prospective research participants are provided the information they need to make decisions that best serve their goals. In my dream world, I would bring these twelve experts together—in person, not virtually!—in a spacious den around a roaring fi e, and would eagerly listen to them discuss among themselves as they spin out the sequels to their stories.

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Commentary

Challenges of Clinical Research Administration During the COVID-19 Pandemic

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Abstract. In early 2020, clinicians and researchers rushed to understand the SARS-CoV-2 virus and how to go about treating and preventing it. Caring for patients while simultaneously learning about a disease not seen before created challenges on several levels. Much of the spotlight was on the researchers doing this critical work; however, these narratives remind us of the enormous effort and commitment shown by IRB members and research administrators responsible for research infrastructure. Despite the sense of urgency and obligation to plan and conduct clinical research during the pandemic, IRBs guaranteed that researchers still adhered to the core ethical principles that protect the rights and welfare of human subjects so that critical research could continue. Many themes emerge in these stories, including the need for flexibility in processes for both staff and research participants and the perception that IRB members serve as "research gatekeepers." With approaches to clinical research evolving, the SARS-CoV-2 pandemic may be the catalyst needed to make sustainable improvements to our research processes, roles, and goals.

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The COVID-19 pandemic first reached the United States in Seattle but it was only a short time later that it appeared in New York City to create a crisis, the scale of which had not been seen before. New York was about to become the epicenter of the pandemic but the magnitude of the crisis and the impact that it was about to have on all of our lives was not immediately clear to most people in the United States regardless of whether you were a clinician, researcher, administrator or the average person on the street.

Central to the challenge was the need to understand the virus, the disease, and how to go about treating and preventing it—and we were literally starting from scratch. This meant caring for patients while simultaneously trying to learn about a disease that had not been seen before, creating challenges on several levels. While much of the spotlight remained on researchers doing this critical work, many things happened behind the scenes that were necessary to keep the research machinery working. These stories remind us of the enormous effort and

commitment shown by individuals and teams that are responsible for much of the research infrastructure—without whom the pandemic would look very different today than it does currently. Reading through these stories from IRB administrators, many common threads emerge as we think about the pandemic's impact and what this might mean for those of us engaged in research. As Stefanie Juell pointed out in these narratives—"pandemics don't last forever," which is fortunate. However, the opportunities to learn from the pandemic will fade with time if allowed to do so—if not, the lessons learnt could serve us well moving forward.

Human Challenges

Like many other non-patient-facing parts of academic medical centers, the IRB staff left campus in March 2020, unclear of when they were coming back. More importantly, they continued their important and mission-critical work remotely through the pandemic, despite being as Juell describes, "exhausted, scared, frustrated, overworked and overwhelmed"—similar to what many of us in healthcare have experienced. The challenges of childcare were front and center as several stories alluded to the challenges of work-life balance—a theme that is consistent across the country—and the need for increased empathy and exibility with team members was widely acknowledged. Empathy and understanding are more meaningful in the smaller actions that demonstrate their presence—i.e., the acceptance of meeting interruptions as nothing more than "cameos" as Edith Paal states. In short, these stories serve well to remind us of the challenges IRB members and research administrators faced in keeping research at the high standards that we have come to expect. We have much to thank them for as they worked through pandemics and earthquakes.

Technology

The invasion of technology into our lives was already occurring at a steady drumbeat prior to the pandemic but who would have thought that "you are on mute" would become one of the most common phrases that we would hear every day. While conferencing technologies have their own challenges, the pandemic, as we have come to experience it this past year, would have been unrecognizable without them. While these technologies have their downsides and challenges, the associated benefits abound as well. As Joan B. Cobb Pettit put it, many "miss the dynamic of in-person IRB meetings" while others "really like not having to commute and dress for the office." The challenges of the pandemic on women have been described at length elsewhere and this ought to force us to rethink our current work models. The need to re-examine these is particularly urgent in academia. However, technologies that facilitated work from home have also helped create opportunities for positive memories that would not have happened otherwise—a 20-minute tickle session is an example of a memory that Jennifer Randles will keep, I suspect, forever.

The speed of adoption in a crisis of new technologies and overcoming the technology inertia that is often associated with academic medical centers and healthcare, in general, was a silver lining. While the descriptions of rapid technology adoption abounded in these stories along with some teething troubles, the absence of descriptions of resistance, reluctance, and failure was perhaps even more telling. We will eventually debate how much of this we want to keep (and we should). However, this experience will hopefully inform how other future technology opportunities will be viewed and maybe there will be less inertia in their adoption.

While the adoption of technology on the administrative side is seen as a clear win, implementing these very same technologies in the research realm created some wins and needs to be accompanied by critical questions. As said so eloquently by de Vos, "we must weigh the need for temporary accommodations versus long-term sustainable solutions." A rush to improve patient care with tools that require highspeed internet connections and smartphones can leave out the very patients who would benefit from them the most (i.e., our most vulnerable patients) (Badawy & Radovic, 2020; S. Nouri, Khoong, Lyles, & Karliner, 2020). Similarly, the rush

to engage in technology to overcome the challenges of the pandemic risks creating an additional hurdle for impoverished individuals and people of color to participate in research (Amin, Rae, Ramirez, & Cox, 2020). Having mere access to the technology may not be enough to remove barriers (S. S. Nouri et al., 2019; Weiss & Eikemo, 2017). For example, an in-person interview in a private office could result in a very different outcome than the same interview over a technology interface where the participant remains within earshot of their family members.

Flexibility in Processes

When Stefanie Juell states that, "The IRB's purpose is not to impede research," there is an implicit recognition that researchers often perceive that the IRB is an impediment to research. We need to think about how we have managed to create this unhelpful characterization of IRBs—an important component of our research infrastructure—as "a dreaded but necessary institutional hoop" or even worse as a "potential obstruction to conducting research" (Jennifer Randles). Many of the stories highlight the need for and subsequent introduction of flexibility that was missing from their processes pre-pandemic.

Recognizing the need for increased flex bility and the need to revisit processes was a common thread among many stories. Shorter amendment forms and other flexibilities that allow for "reduc[ing] the number of individual submissions coming in," (Stefanie Juell) or for that matter, implementing the "probably overdue" electronic signature (Brian Moore) are all examples of process implementations that were either considered or accelerated because of the pandemic.

The introduction of flexibility and the movement away from paternalism, at least when participants are not part of vulnerable populations, are examples of what a forced re-examination of processes and assumptions can result in. The real question is, how many of these changes are going to be allowed to persist after the pandemic? There are lessons to be learnt from these changes that ought to inform further review and revisions of processes—such that additional changes are identified that would benefit participants in particular but research teams as well.

Remote Consents

The ability to obtain consent without an in-person conversation was necessitated by the limitations created by the large number of critically ill, sedated, and ventilated patients—coupled with restrictions on visitors. Perhaps, it is often forgotten that consents for procedures and other clinical activity are often obtained remotely in clinical medicine from family and next of kin all the time in an appropriate and robust manner. These consents are obtained for the most complex of procedures and yet IRBs seem reluctant to embrace this approach.

While the intent of restrictions of how and when consent can be obtained is self-evident, the unintended negative consequences are sometimes less obvious and often overlooked. In her narrative, Hallie Kassan writes that there was increased recognition that criteria more stringent than the Common Rule at an organizational level were not helpful or in the participants' best interest. Similarly, IRBs that "advocated very strongly in the past for in-person informed consent discussions" (Sujatha Sridhar) moved to recognize that remote consents could be complete and thorough. These changes are likely to benefit both study participants and research teams if allowed to remain in place post-pandemic.

There was concern expressed about the adverse impact of information in the media–graphic or otherwise—and its impact on informed consent. Prognostic information, whether it comes in the form of a study that provides 5-year survival estimates or graphic images in the press, will always inform the willingness of patients to participate in studies—and it probably ought to. In order to make informed choices, patients need to have the information that provides them the broader context to be able to do. Just as we try to move away from paternalism in medicine and empower patients to participate in decision making about their healthcare choices, we need to recognize that these very same individuals should be considered capable of

understanding the context in which they are being approached to participate in studies.

Gatekeepers

While IRBs are charged with ensuring the safety of the study participants, it was interesting to note that many stories touched on their perceived role as research gatekeepers. The folly of the research effort that went into studying hydroxychloroquine is less a failure on clinical researchers and IRBs than of the peer-review process that provided the initial data suggesting a benefit where there wasn't any. Let's pause to think what those 104 studies in different subsets of individuals in different locations would have meant had hydroxychloroquine *actually* been an effective therapeutic intervention in at least a subset of individuals. Decisions to launch these studies and participate were not an act of desperation. They were based on the evidence at the time that suggested hydroxychloroquine might work and the need to know if it did—especially given that it has been taken safely by millions of patients for both malaria and lupus.

In the early days of the pandemic, when our understanding of the disease was extremely limited, clinicians were faced with the need to reach for anything that might work. This cannot be equated to circumstances where desperate attempts or offers were made for individual patients. With healthcare systems being overwhelmed and a war-like footing needed at the bedside to care for patients, potential discoveries of successfully repurposed drugs held the potential to save thousands of lives—and would have had significant implications for everyone. The idea that IRBs ought to act as gatekeepers that call into question what to study or that observational research should take a back seat is troubling. Much of what we learnt early in the pandemic resulted from astute bedside observations and the identi - cation of key findings in large observational datasets. While the question of which studies should be undertaken is an important one, shouldn't these questions be asked by the expert clinicians and researchers who have a better grasp on the knowledge gaps and how a particular study might inform next steps—or should it be the IRB? Doesn't this contradict the notion that IRBs have a "duty to approve sound science that is based on an assessment of submitted materials—not based on political pressures or even external circumstances," as Stefanie Juell states in her narrative? Is there really a difference between the goals of research and the goals of clinical medicine when there is a complete absence of knowledge of what we were faced with? When something as fundamental as the appropriate timing of intubation and mechanical ventilation is unknown, does therapeutic misconception even exist? Shouldn't we study everything—every little intervention or lack thereof—to understand what we are facing? Shouldn't every action or inaction be subject to scrutiny as we expand our understanding of what we should and should not be doing? If that scrutiny is called research, then isn't that divide somewhat arbitrary and potentially misleading?

Should clinicians have done more in the form of randomized controlled trials rather than choosing to make certain therapeutic maneuvers into the standard of care early in the pandemic? Most would probably agree today in hindsight, but we have to ask what systemic issues led us in the opposite direction. Certainly, some of this was caused by the desire to do *something . . . , anything . . .* because that seemed better than doing *nothing . . .* or so it seemed at the time. The extent to which the choices made are a result of the regulatory burdens and process challenges, as well as how physicians are taught to create or even evaluate reliable data, will need to be studied further. The idea, often perpetuated by medical school deans and department chairs, that only those in basic science labs deserve the moniker of "physician-scientist" and the attendant biases associated with this idea have likely contributed to this. How we do clinical research, particularly in difficult circumstances, is an important question that should inform future process development. With large datasets, as well as rapidly changing technology and data science, the role and value of observational data are changing. With the rapid growth of electronic systems that can capture extraordinary amounts of data and metadata along with the expansion of tools available for analysis,

the volume and value of this type of work will only grow—and has the potential to change the paradigm of how we learn in medicine. Clinical research approaches are evolving, and the pandemic may just be the stimulus needed to re-evaluate processes, roles, and goals.

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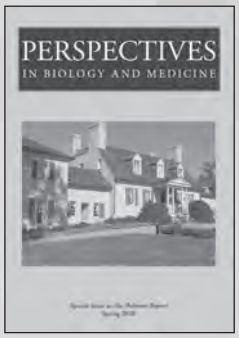

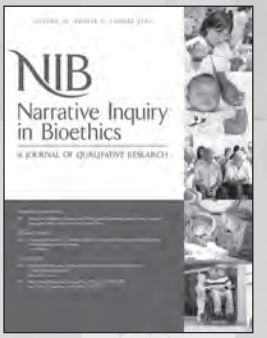

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